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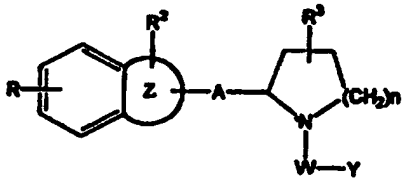
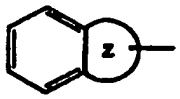
(54) Title: AROMATIC AMIDINE DERIVATIVES USEFUL AS SELECTIVE THROMBIN INHIBITORS



(I)



(a)

(57) Abstract

The present invention relates to a novel thrombin inhibitor which is effective even when orally administered. More specifically, the present invention relates to an aromatic amidine derivative represented by formula (I) and the salts thereof, which show potent selective inhibitory activity for thrombin in which (a), R, R^1, R^2, R^3, A, W, Y and n are defined as described in the specification.

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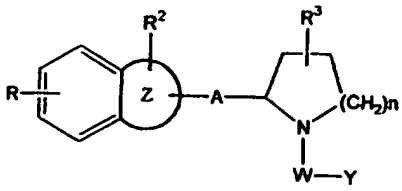
AROMATIC AMIDINE DERIVATIVES USEFUL AS SELECTIVE THROMBIN INHIBITORS

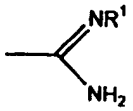
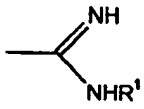
TECHNICAL FIELD

The present invention relates a novel thrombin inhibitor which is effective even when orally administered. More specifically, the present invention relates to an aromatic amidine derivative represented by formula (I) and the salts thereof, which show potent selective inhibitory activity for thrombin:

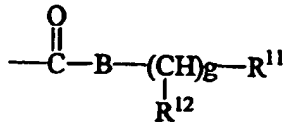


(I)

in which

R represents a group of formula  or  , wherein

R^1 represents hydrogen, hydroxy, alkyl, alkoxy, alkylcarbonyl, alkylcarbonyloxy, aralkoxycarbonyl, or a radical of formula (a),



(a)

wherein

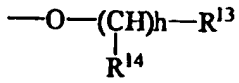
B represents oxygen or sulfur;

R^{11} and R^{12} independently of one another represent hydrogen, haloalkyl, alkylcarbonyloxy, dialkylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

g denotes an integer of 0 to 3;

R^2 represents hydrogen, hydroxy, halogen, carboxy, aminocarbonyl, alkyl, alkoxy, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkylsulfonyl, carboxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^3 represents hydrogen, halogen, alkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, carboxy, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, or a radical of formula (b),

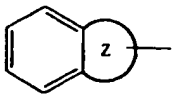


(b)

wherein

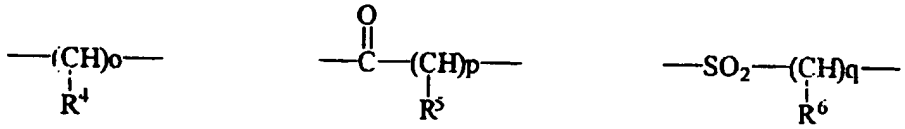
R^{13} and R^{14} independently of one another represent hydrogen, alkyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

h denotes an integer of 0 to 3;

the group of formula  represents a radical selected from the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, naphthyl, tetrahydronaphthyl, indanyl, dihydrobenzofuranyl and dihydrobenzothienyl;

A represents a saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, alkoxycarbonyl and alkoxycarbonylalkyl;

W represents a group of formula (c), (d) or (e),



(c) (d) (e)

wherein

o, p and q independently of one another denote an integer of 0 to 3,

R^4, R^5 and R^6 independently of one another represent hydrogen, hydroxy, carboxy, alkoxycarbonyl, substituted or unsubstituted arylsulfonyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),

(f) (g) (h)

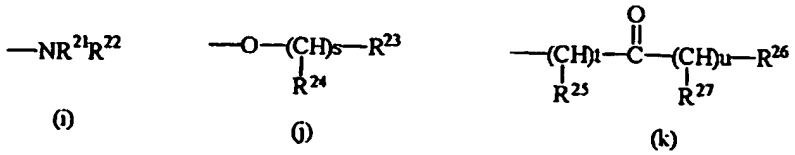
wherein

R^{15}, R^{16}, R^{17} and R^{18} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, aminocarbonylalkyl, alkoxycarbonylalkyl, substituted or unsubsituted arylsulfonyl, substituted or unsubstituted aralkyl, or substituted or unsubsituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or alkoxycarbonyl, or represents 3- to 7-memebered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings; and

r denotes an integer of 0 to 3;

Y represents hydrogen or a 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings and which may be substituted on any atom of the ring with a substituent selected from the group consisting of oxygen, halogen, nitro, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



(i) (j) (k)

wherein

R^{21} and R^{22} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, alkoxycarbonyl, or 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings;

R^{25}, R^{26} and R^{27} independently of one another represent hydrogen, hydroxy, thio, amino, carboxy, aminocarbonyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfonylamino, alkenyl, alkoxycarbonylamino, cycloalkylamino, alkoxycarbonylalkylamino, substituted or unsubstituted arylsulfonylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

s denotes an integer of 0 to 3;

t denotes an integer of 0 to 6; and

u denotes an integer of 0 to 8; and

n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be straight or branched.

The present invention also relates to a process for preparation of the compound of formula (I), and a thrombin inhibitor composition containing the compound of formula (I) as an active component.

BACKGROUND ART

Thrombosis is a pathological process in which platelets aggregation or a fibrin clot occludes a blood vessel. Anticoagulants interfere

with fibrin formation and are used for prophylaxis of thrombosis.

The blood coagulation system involves a number of zymogens (inactive enzymes) that are activated through a cascade of enzymatic reactions. The final step in coagulation is the formation of the fibrin clot from fibrinogen by a trypsin-like serine protease thrombin, which in turn is generated from prothrombin by the action of factor Xa. Accordingly, the blood coagulation enzyme thrombin plays a central role in hemostasis and thrombosis. Thrombin inhibitors are therefore expected to be effective anticoagulants by inhibition of platelets, fibrin formation and fibrin stabilization. It also activates factor V and factor VIII in a positive feed back reaction.

In recent years, numerousthrombin inhibitors have been developed as potential antithrombotic and anticoagulant agents, for example, tripeptide derivatives such as PPACK [D-Phe-Pro-Arg-CH_2Cl, Thromb. Res., 14, 969 (1979)], D-Phe-Pro-Arg, Boc-D-Phe-Pro-Arg, and D-MePhe-Pro-Arg [J. Med. Chem., 33, 1729 (1990)], DuP-714 [Ac-(D)-Phe-Pro-boroArg-OH, J. Biol. Chem., 265, 18289 (1990)], Efegatran [D-MePhe-Pro-Arg · H_2SO_4, Thromb. Haemost., 67, 325 (1992)], Inogatran [HOOC-CH_2-(R)Cha-Pic-Nag, where Cha : cyclohexylamine, Pic : pipecolic acid and Nag : noragmatine, WO 93/11152, Blood Coag. Fibrinol., 7, 69 (1996)] and CVS-1123 [$(CH_3CH_2CH_2)_2$-CHCO-Asp(OCH_3)-Pro-Arg, WO 93/15756] and piperidine amide derivatives such as Argatroban [US 4258192, Thromb. Haemost., 18, 13 (1992)] and NAPAP [J. Biol. Chem., 266, 20085 (1991)]. But, they are not necessarily sufficient for practical use in view of oral bioavailability, inhibition selectivity for thrombin over other serine proteases, stability, duration of action and toxicity at the therapeutic dosages.

In view of the above, the present inventors have conducted intensive studies to develop potent thrombin inhibitors which are orally bioavailable, selective in inhibition of thrombin over other serine proteases and sufficient for practical use. As a result of such efforts, we have found that the compound of formula (I) exhibits excellent

thrombin inhibitory activity even when orally administered and has a high selectivity for thrombin in comparison to trypsin, and have thereby completed the present invention.

DISCLOSURE OF THE INVENTION

The present invention relates to an aromatic amidine derivative of formula (I), as defined above, and pharmaceutically acceptable salts thereof.

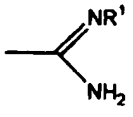
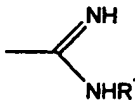
In addition, the present invention relates to a process for preparation of the compound of formula (I).

The present invention further relates to a thrombin inhibitor composition containing the compound of formula (I) or its pharamceutically acceptable salts as an active component.

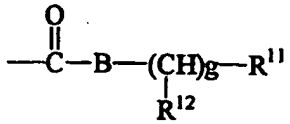
BEST MODE FOR CARRYING OUT THE INVENTION

The compound according to the present invention is represented by formula (I) as defined above.

Preferred compound of formula (I) according to the present invention includes those, in which

R represents a group of formula  or  , wherein

R^1 represents hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_4 alkyl-carbonyl, C_2-C_4 alkylcarbonyloxy, or a radical of formula (a),



(a)

wherein

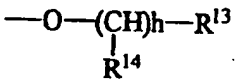
B represents oxygen or sulfur,

R^{11} and R^{12} independently of one another represents hydrogen, C_1-C_4 haloalkyl, C_2-C_4 alkylcarbonyloxy, C_2-C_6 dialkylamino, or substituted or unsubstituted 6-membered carbocyclic ring, and

g denotes an integer of 0 to 3;

R^2 represents hydrogen, halogen, carboxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 aminoalkyl, C_2-C_4 alkylcarbonyl, C_1-C_4 alkylsulfonyl, C_2-C_4 carboxyalkyl, C_2-C_4 aminocarbonylalkyl or C_3-C_7 alkoxycarbonylalkyl;

R^3 represents hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_2-C_4 carboxyalkyl, C_3-C_7 alkoxycarbonylalkyl, or a radica of formula (b),

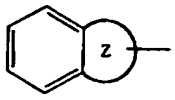


(b)

wherein

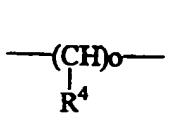
R^{13} and R^{14} independently of one another represent hydrogen or phenyl, and

h denotes an integer of 0 to 1;

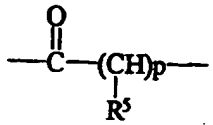
the group of formula  represents a radical selected from the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl and naphthyl;

A represents saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, C_1-C_4 hydroxyalkyl and C_2-C_4 alkoxycarbonyl;

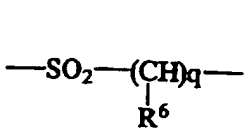
W represents a group of formula (c), (d) or (e),



(c)



(d)

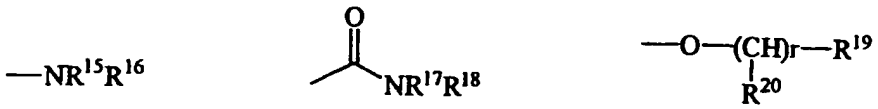


(e)

wherein

o, p and q independently of one another denote an integer of 0 to 3,

R^4, R^5 and R^6 independently of one another represent hydrogen, hydroxy, carboxy, C_2-C_4 alkoxycarbonyl, phenylsulfonyl, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),



(f) (g) (h)

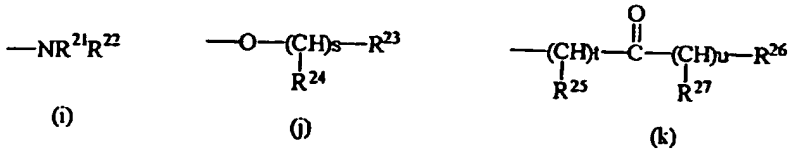
wherein

R^{15}, R^{16}, R^{17} and R^{18} independently of one another represent hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylsulfonyl, C_2-C_4 carboxyalkyl, C_2-C_4 alkylcarbonyl, C_2-C_4 aminocarbonylalkyl, C_3-C_7 alkoxycarbonylalkyl, or substituted or unsubsituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or C_2-C_4 alkoxycarbonyl, or represents 5- to 6-memebered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring, and

r denotes an integer of 0 to 3;

Y represents hydrogen, or represents 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring and which can be substituted on any atom of the ring with substituent selected from the group consisting of oxygen, halogen, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkylsulfonyl, phenylsulfonyl, substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



(i) (j) (k)

wherein

R^{21} and R^{22} independently of one another represent hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylsulfonyl, C_2-C_5 carboxyalkyl, C_2-C_5 alkylcarbonyl, C_3-C_7 alkoxycarbonylalkyl or phenylsulfonyl,

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, C_2-C_4 alkoxycarbonyl, or 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

R^{25}, R^{26} and R^{27} independently of one another represents hydrogen hydroxy, thio, amino, carboxy, aminocarbonyl, C_1-C_4 alkoxy, C_2-C_4 alkoxycarbonyl, C_1-C_4 alkylamino, C_1-C_4 alkylsulfonylamino, C_2-C_5 alkenyl, C_2-C_4 alkoxycarbonylamino, C_3-C_6 alkoxycarbonylalkylamino, C_3-C_6 cycloalkylamino, phenylsulfonylamino, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

s denotes an integer of 0 to 3,

t denotes an integer of 0 to 6, and

u denotes an integer of 0 to 8, and

n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be strainght or branched.

Typical examples of the compound of formula (I) which can be provided by the present invention are listed in the following Table 1.

Table 1.

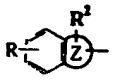
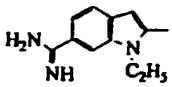
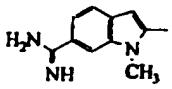
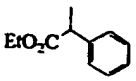
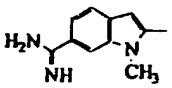
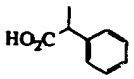
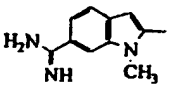
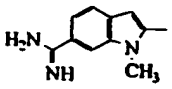
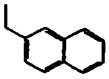
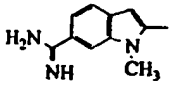
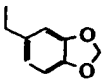
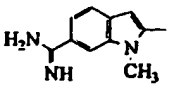
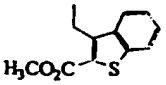
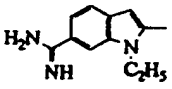
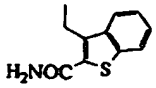
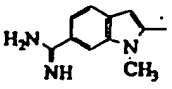
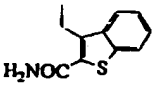
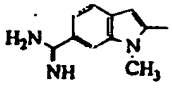
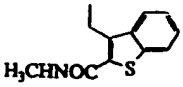
compound No.		A	R^3	n	W - Y
1		CH_2CH_2	H	1	
2		CH_2CH_2	H	1	
3		CH_2CH_2	H	1	
4		CH_2CH_2	H	1	
5		CH_2CH_2	H	1	
6		CH_2CH_2	H	1	
7		CH_2CH_2	H	1	
8		CH_2CH_2	H	1	
9		CH_2CH_2	H	1	
10		CH_2CH_2	H	1	

Table 1. (continued)

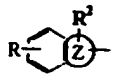
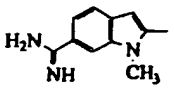
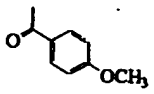
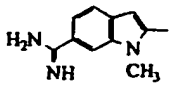
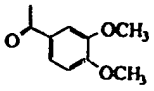
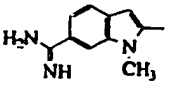
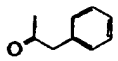
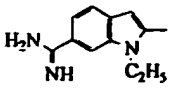
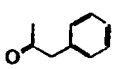
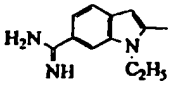
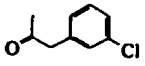
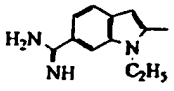
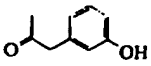
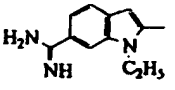
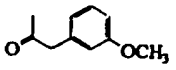
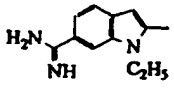
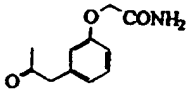
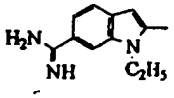
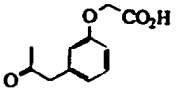
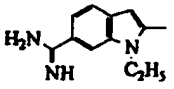
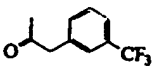
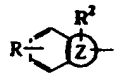
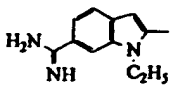
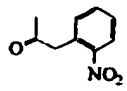
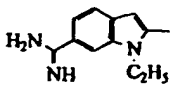
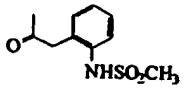
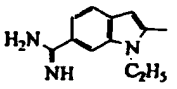
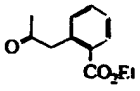
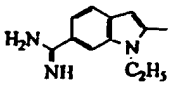
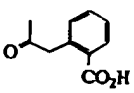
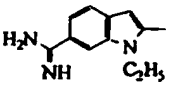
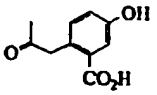
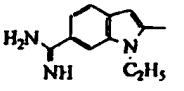
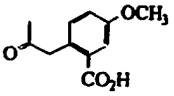
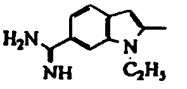
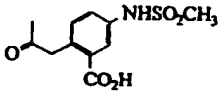
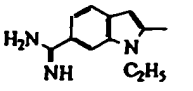
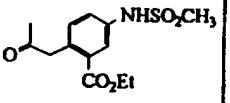
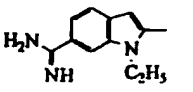
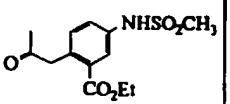
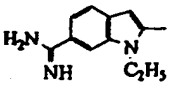
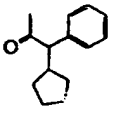
compound No.		A	R^3	n	W - Y
11		CH_2CH_2	H	1	
12		CH_2CH_2	H	1	
13		CH_2CH_2	H	1	
14		CH_2CH_2	H	1	
15		CH_2CH_2	H	1	
16		CH_2CH_2	H	1	
17		CH_2CH_2	H	1	
18		CH_2CH_2	H	1	
19		CH_2CH_2	H	1	
20		CH_2CH_2	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
21		CH_2CH_2	H	1	
22		CH_2CH_2	H	1	
23		CH_2CH_2	H	1	
24		CH_2CH_2	H	1	
25		CH_2CH_2	H	1	
26		CH_2CH_2	H	1	
27		CH_2CH_2	H	1	
28		CH_2CH_2	H	1	
29		CH_2CH_2	H	2	
30		CH_2CH_2	H	1	

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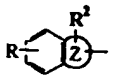
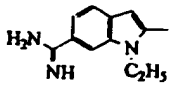
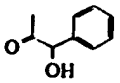
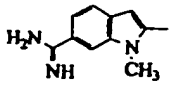
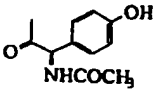
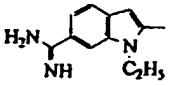
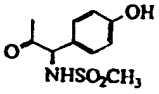
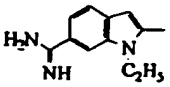
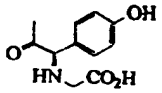
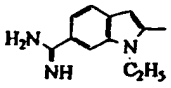
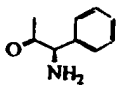
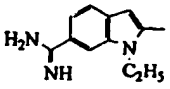
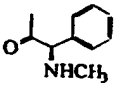
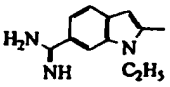
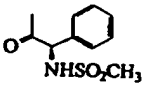
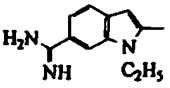
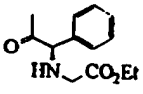
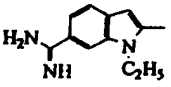
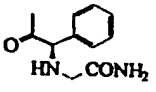
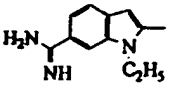
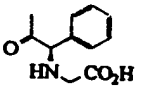
compound No.		A	R^3	n	W - Y
31		CH_2CH_2	H	1	
32		CH_2CH_2	H	1	
33		CH_2CH_2	H	1	
34		CH_2CH_2	H	1	
35		CH_2CH_2	H	1	
36		CH_2CH_2	H	1	
37		CH_2CH_2	H	1	
38		CH_2CH_2	H	1	
39		CH_2CH_2	H	1	
40		CH_2CH_2	H	1	

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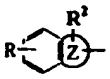
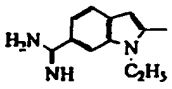
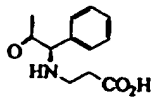
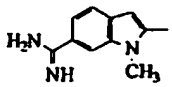
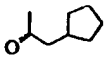
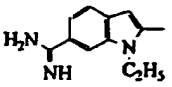
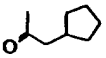
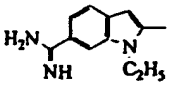
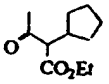
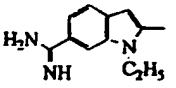
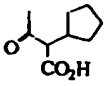
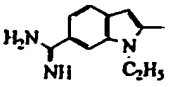
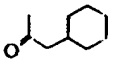
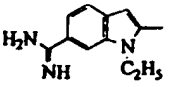
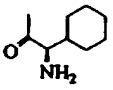
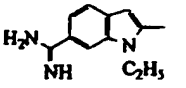
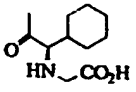
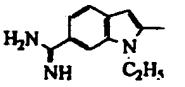
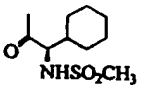
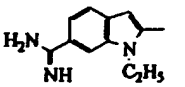
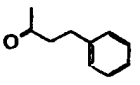
compound No.		A	R^3	n	W - Y
41		CH_2CH_2	H	1	
42		CH_2CH_2	H	1	
43		CH_2CH_2	H	1	
44		CH_2CH_2	H	1	
45		CH_2CH_2	H	1	
46		CH_2CH_2	H	1	
47		CH_2CH_2	H	1	
48		CH_2CH_2	H	1	
49		CH_2CH_2	H	1	
50		CH_2CH_2	H	1	

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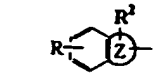
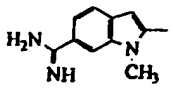
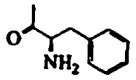
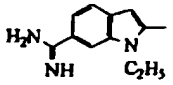
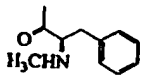
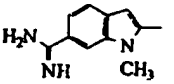
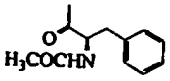
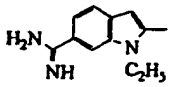
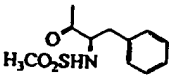
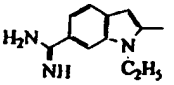
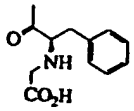
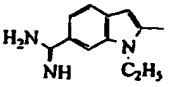
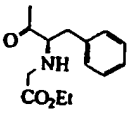
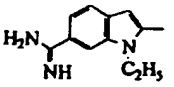
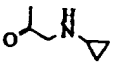
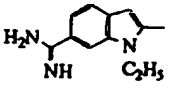
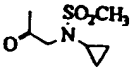
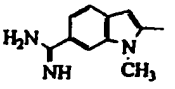
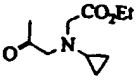
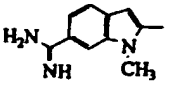
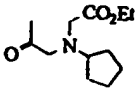
compound No.		A	R^3	n	W - Y
51		CH_2CH_2	H	1	
52		CH_2CH_2	H	1	
53		CH_2CH_2	H	1	
54		CH_2CH_2	H	1	
55		CH_2CH_2	H	1	
56		CH_2CH_2	H	1	
57		CH_2CH_2	H	1	
58		CH_2CH_2	H	1	
59		CH_2CH_2	H	1	
60		CH_2CH_2	H	1	

Table 1. (continued)

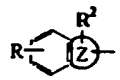
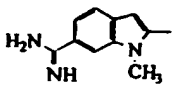
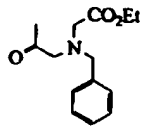
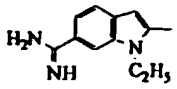
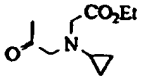
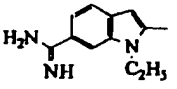
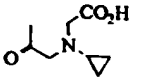
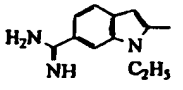
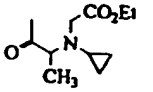
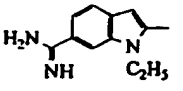
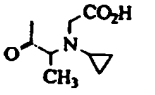
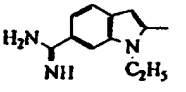
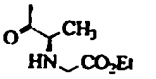
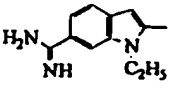
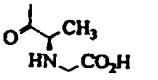
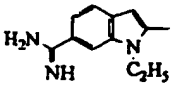
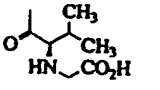
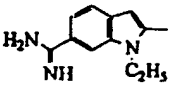
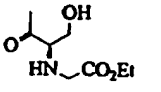
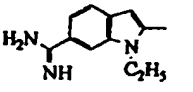
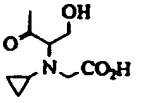
compound No.		A	R^3	n	W - Y
61		CH_2CH_2	H	1	
62		CH_2CH_2	H	1	
63		CH_2CH_2	H	1	
64		CH_2CH_2	H	1	
65		CH_2CH_2	H	1	
66		CH_2CH_2	H	1	
67		CH_2CH_2	H	1	
68		CH_2CH_2	H	1	
69		CH_2CH_2	H	1	
70		CH_2CH_2	H	1	

Table 1. (continued)

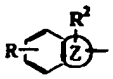
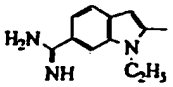
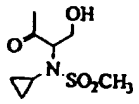
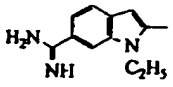
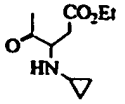
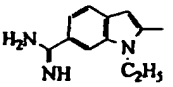
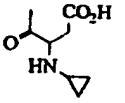
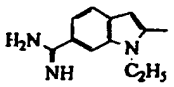
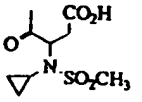
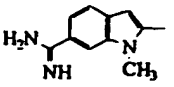
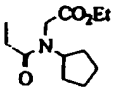
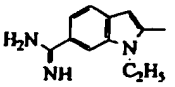
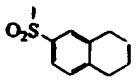
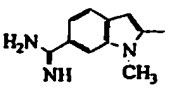
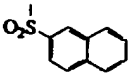
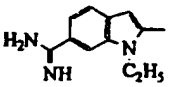
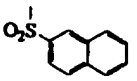
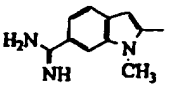
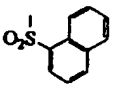
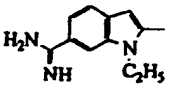
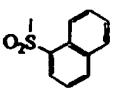
compound No.		A	R^3	n	W - Y
71		CH_2CH_2	H	1	
72		CH_2CH_2	H	1	
73		CH_2CH_2	H	1	
74		CH_2CH_2	H	1	
75		CH_2CH_2	H	1	
76		CH_2CH_2	H	1	
77		CH_2CH_2	H	1	
78		CH_2CH_2	H	2	
79		CH_2CH_2	H	1	
80		CH_2CH_2	H	2	

Table 1. (continued)

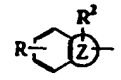
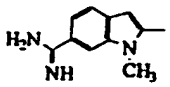
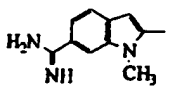
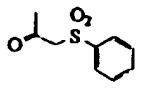
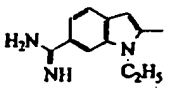
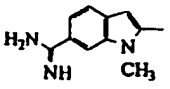
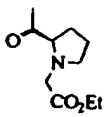
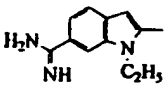
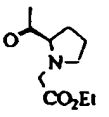
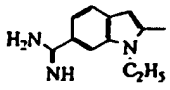
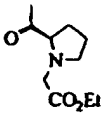
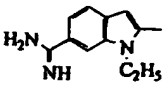
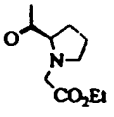
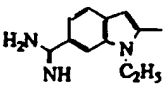
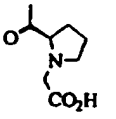
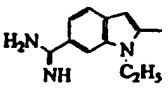
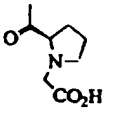
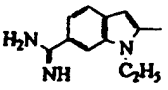
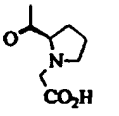
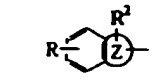
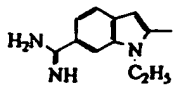
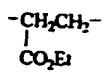
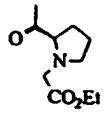
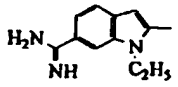
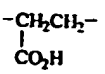
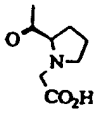
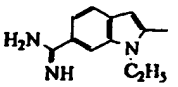
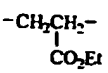
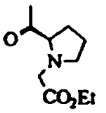
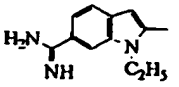
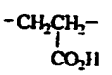
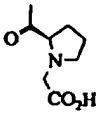
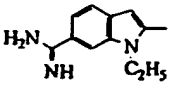
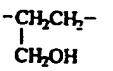
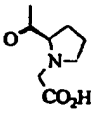
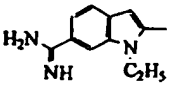
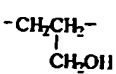
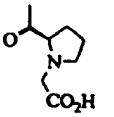
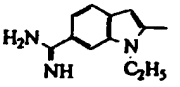
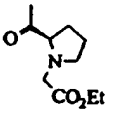
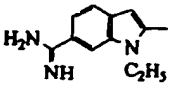
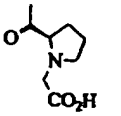
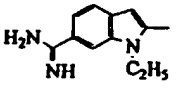
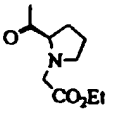
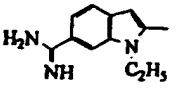
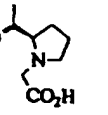
compound No.		A	R^3	n	W - Y
81		CH_2CH_2	H	1	
82		CH_2CH_2	H	1	
83		CH_2CH_2	H	1	
84		CH_2CH_2	H	1	
85		CH_2CH_2	H	0	
86		CH_2CH_2	H	1	
87		CH_2CH_2	H	2	
88		CH_2CH_2	H	1	
89		CH_2CH_2	H	2	
90		$CH_2CH_2CH_2$	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
91			H	1	
92			H	1	
93			H	1	
94			H	1	
95			H	1	
96			H	1	
97		CH_2CH_2	4(S) -CH_3	1	
98		CH_2CH_2	4(S) -CH_3	1	
99		CH_2CH_2	4(S) -OCH_3	1	
100		CH_2CH_2	4(S) -OPh	1	

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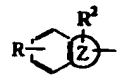
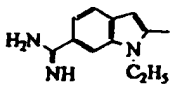
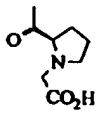
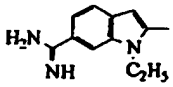
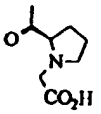
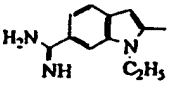
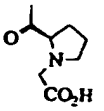
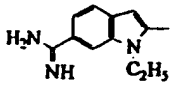
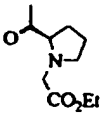
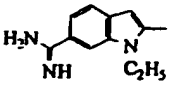
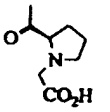
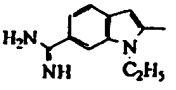
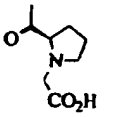
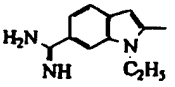
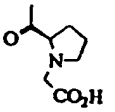
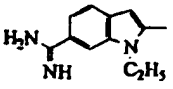
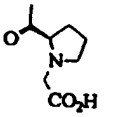
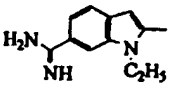
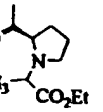
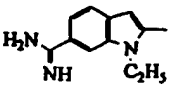
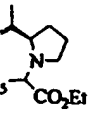
compound No.		A	R^3	n	W - Y
101		CH_2CH_2	4(S) -OCH_2Ph	1	
102		CH_2CH_2	4 -OH	1	
103		CH_2CH_2	4 -F	1	
104		CH_2CH_2	4 -CH_2CO_2Et	1	
105		CH_2CH_2	4 -CH_2CO_2H	1	
106		CH_2CH_2	4 -CH_2CH_2OH	1	
107		CH_2CH_2	4 -$CH_2CH_2CO_2H$	1	
108		CH_2CH_2	4 -$CH_2CH_2CH_2OH$	1	
109		CH_2CH_2	H	1	
110		CH_2CH_2	H	1	

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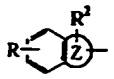
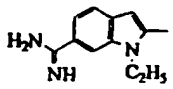
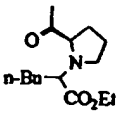
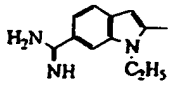
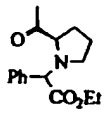
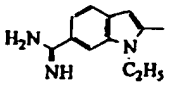
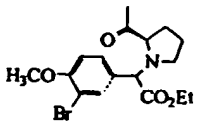
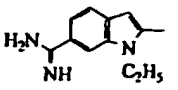
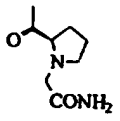
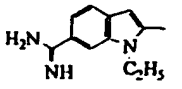
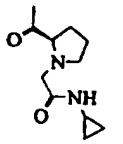
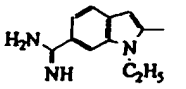
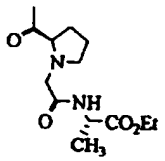
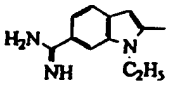
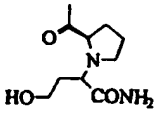
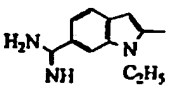
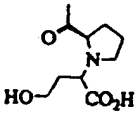
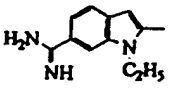
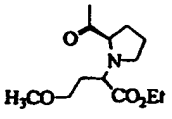
compound No.		A	R^3	n	W - Y
111		CH_2CH_2	H	1	
112		CH_2CH_2	H	1	
113		CH_2CH_2	H	1	
114		CH_2CH_2	H	1	
115		CH_2CH_2	H	1	
116		CH_2CH_2	H	1	
117		CH_2CH_2	H	1	
118		CH_2CH_2	H	1	
119		CH_2CH_2	H	1	

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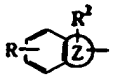
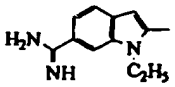
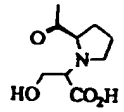
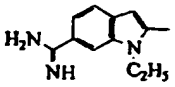
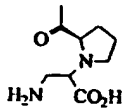
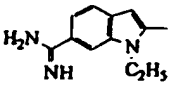
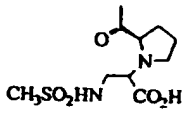
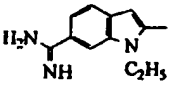
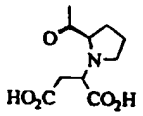
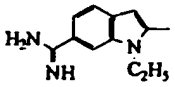
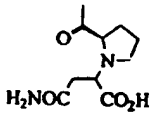
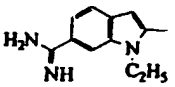
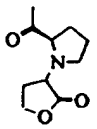
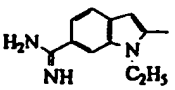
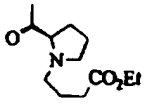
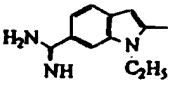
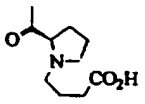
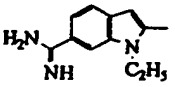
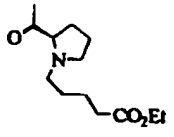
compound No.		A	R^3	n	W - Y
120		CH_2CH_2	H	1	
121		CH_2CH_2	H	1	
122		CH_2CH_2	H	1	
123		CH_2CH_2	H	1	
124		CH_2CH_2	H	1	
125		CH_2CH_2	H	1	
126		CH_2CH_2	H	1	
127		CH_2CH_2	H	1	
128		CH_2CH_2	H	1	

Table 1. (continued)

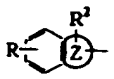
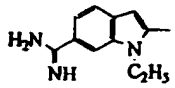
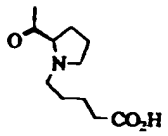
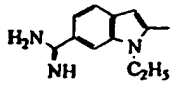
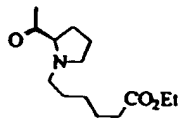
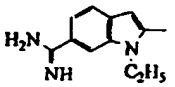
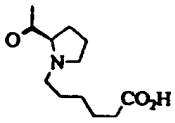
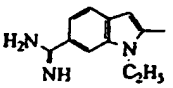
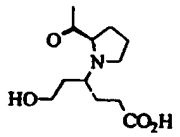
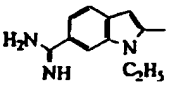
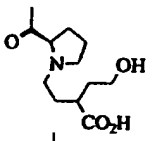
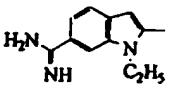
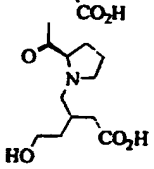
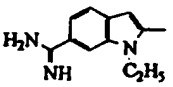
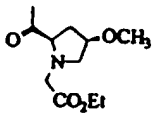
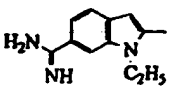
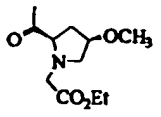
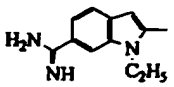
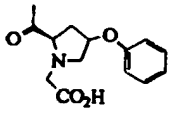
compound No.		A	R^3	n	W - Y
129		CH_2CH_2	H	1	
130		CH_2CH_2	H	1	
131		CH_2CH_2	H	1	
132		CH_2CH_2	H	1	
133		CH_2CH_2	H	1	
134		CH_2CH_2	H	1	
135		CH_2CH_2	H	1	
136		CH_2CH_2	H	2	
137		CH_2CH_2	H	2	

Table 1. (continued)

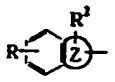
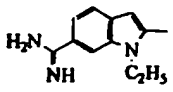
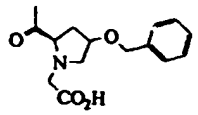
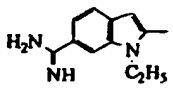
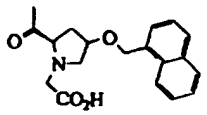
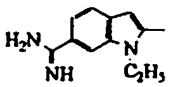
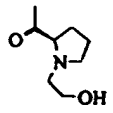
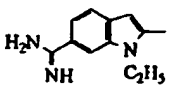
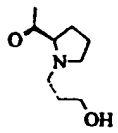
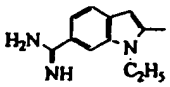
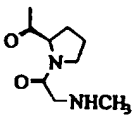
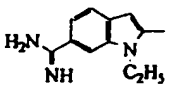
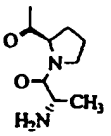
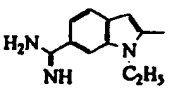
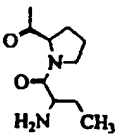
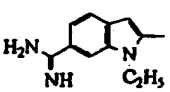
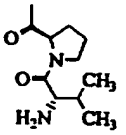
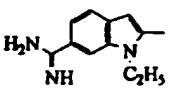
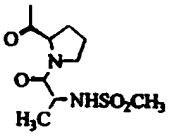
compound No.		A	R^3	n	W - Y
138		CH_2CH_2	H	2	
139		CH_2CH_2	H	2	
140		CH_2CH_2	H	1	
141		CH_2CH_2	H	1	
142		CH_2CH_2	H	1	
143		CH_2CH_2	H	1	
144		CH_2CH_2	H	1	
145		CH_2CH_2	H	1	
146		CH_2CH_2	H	1	

Table 1. (continued)

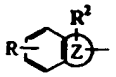
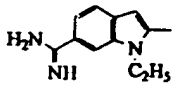
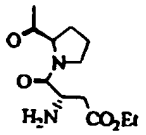
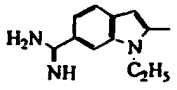
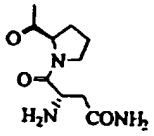
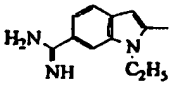
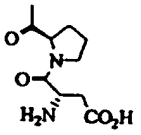
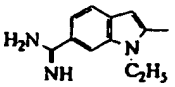
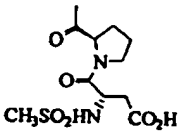
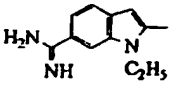
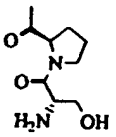
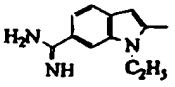
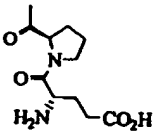
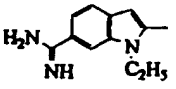
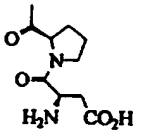
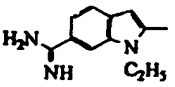
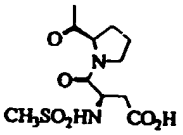
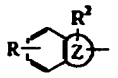
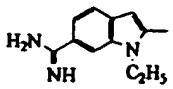
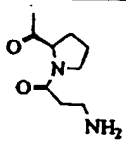
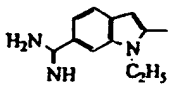
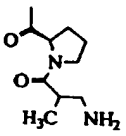
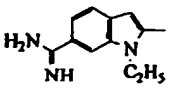
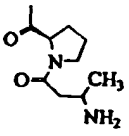
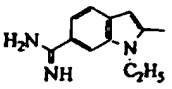
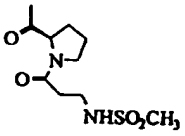
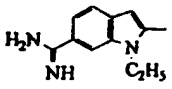
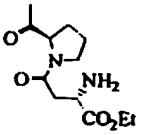
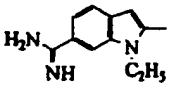
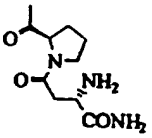
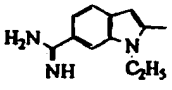
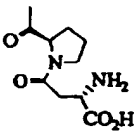
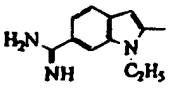
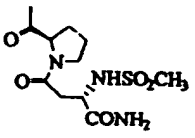
compound No.		A	R^3	n	W - Y
147		CH_2CH_2	H	1	
148		CH_2CH_2	H	1	
149		CH_2CH_2	H	1	
150		CH_2CH_2	H	1	
151		CH_2CH_2	H	1	
152		CH_2CH_2	H	1	
153		CH_2CH_2	H	1	
154		CH_2CH_2	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
155		CH_2CH_2	H	1	
156		CH_2CH_2	H	1	
157		CH_2CH_2	H	1	
158		CH_2CH_2	H	1	
159		CH_2CH_2	H	1	
160		CH_2CH_2	H	1	
161		CH_2CH_2	H	1	
162		CH_2CH_2	H	1	

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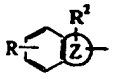
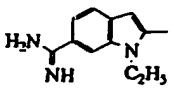
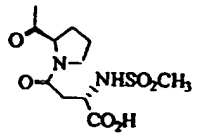
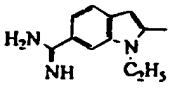
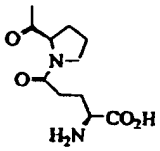
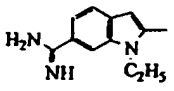
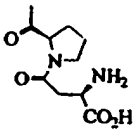
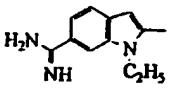
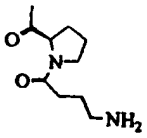
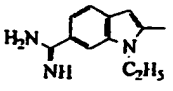
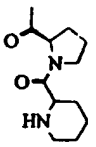
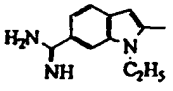
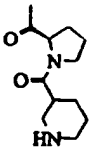
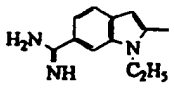
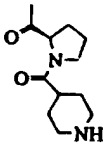
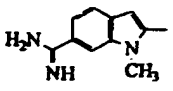
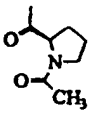
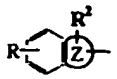
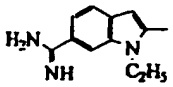
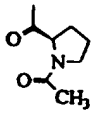
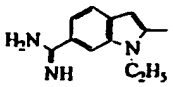
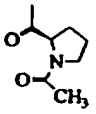
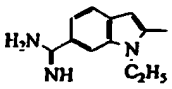
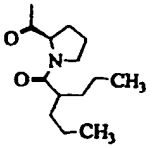
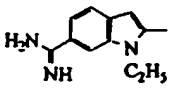
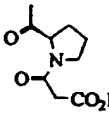
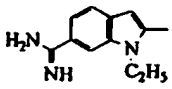
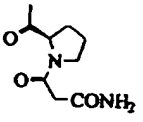
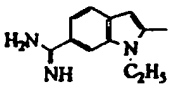
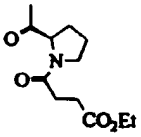
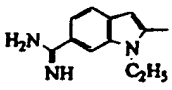
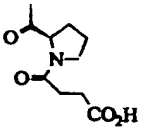
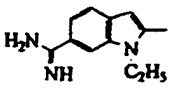
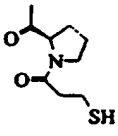
compound No.		A	R^3	n	W - Y
163		CH_2CH_2	H	1	
164		CH_2CH_2	H	1	
165		CH_2CH_2	H	1	
166		CH_2CH_2	H	1	
167		CH_2CH_2	H	1	
168		CH_2CH_2	H	1	
169		CH_2CH_2	H	1	
170		CH_2CH_2	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
171		CH_2CH_2	H	1	
172		CH_2CH_2	4 $-CH_2CO_2H$	1	
173		CH_2CH_2	H	1	
174		CH_2CH_2	H	1	
175		CH_2CH_2	H	1	
176		CH_2CH_2	H	1	
177		CH_2CH_2	H	1	
178		CH_2CH_2	H	1	

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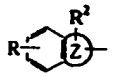
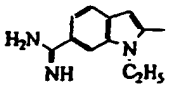
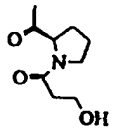
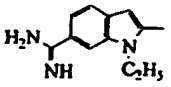
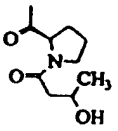
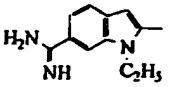
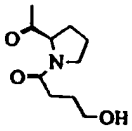
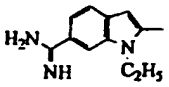
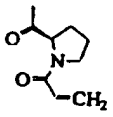
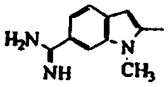
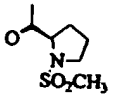
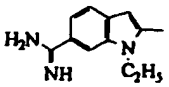
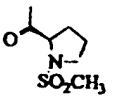
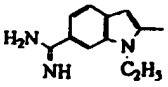
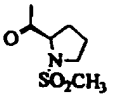
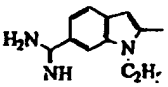
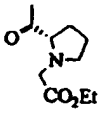
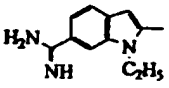
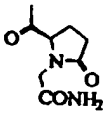
compound No.		A	R^3	n	W - Y
179		CH_2CH_2	H	1	
180		CH_2CH_2	H	1	
181		CH_2CH_2	H	1	
182		CH_2CH_2	H	1	
183		CH_2CH_2	H	1	
184		CH_2CH_2	H	1	
185		CH_2CH_2	4 -CH_2CO_2H	1	
186		CH_2CH_2	H	1	
187		CH_2CH_2	H	1	

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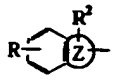
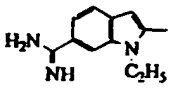
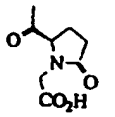
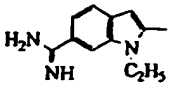
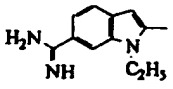
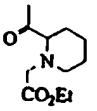
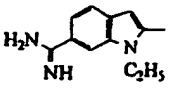
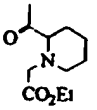
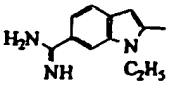
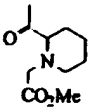
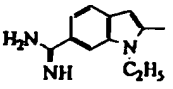
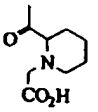
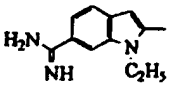
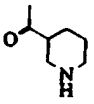
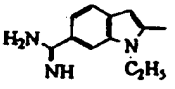
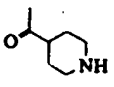
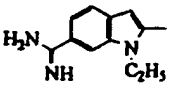
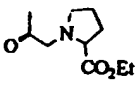
compound No.		A	R^3	n	W - Y
188		CH_2CH_2	H	1	
189		CH_2CH_2	H	1	
190		CH_2CH_2	H	1	
191		CH_2CH_2	H	2	
192		CH_2CH_2	H	1	
193		CH_2CH_2	H	1	
194		CH_2CH_2	H	1	
195		CH_2CH_2	H	1	
196		CH_2CH_2	H	1	

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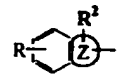
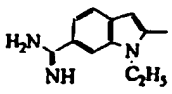
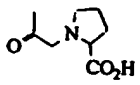
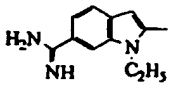
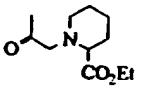
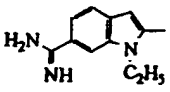
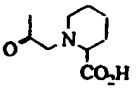
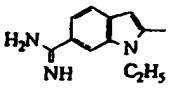
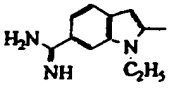
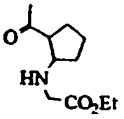
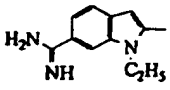
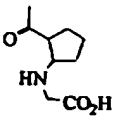
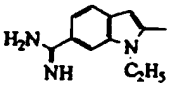
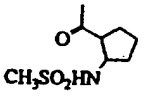
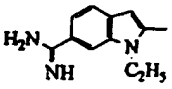
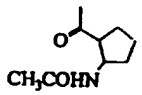
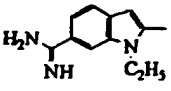
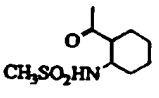
compound No.		A	R^3	n	W - Y
197		CH_2CH_2	H	1	
198		CH_2CH_2	H	1	
199		CH_2CH_2	H	1	
200		CH_2CH_2	H	1	
201		CH_2CH_2	H	1	
202		CH_2CH_2	H	1	
203		CH_2CH_2	H	1	
204		CH_2CH_2	H	1	
205		CH_2CH_2	H	1	

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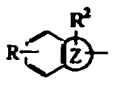
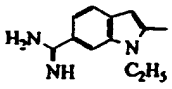
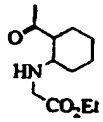
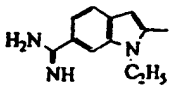
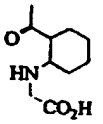
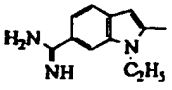
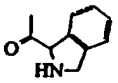
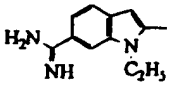
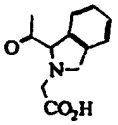
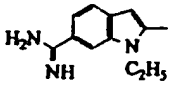
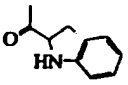
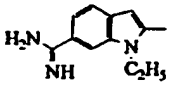
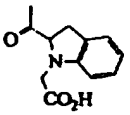
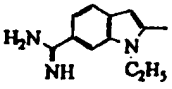
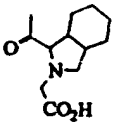
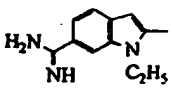
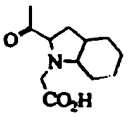
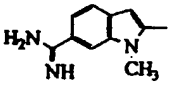
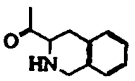
compound No.		A	R^3	n	W - Y
206		CH_2CH_2	H	1	
207		CH_2CH_2	H	1	
208		CH_2CH_2	H	2	
209		CH_2CH_2	H	2	
210		CH_2CH_2	H	2	
211		CH_2CH_2	H	2	
212		CH_2CH_2	H	2	
213		CH_2CH_2	H	2	
214		CH_2CH_2	H	1	

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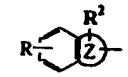
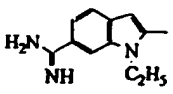
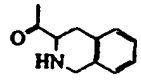
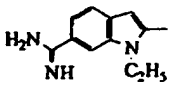
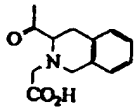
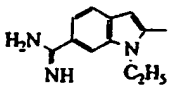
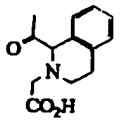
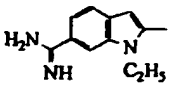
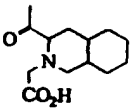
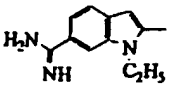
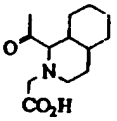
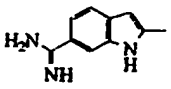
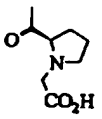
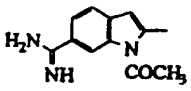
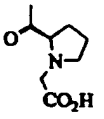
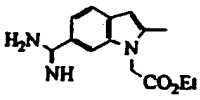
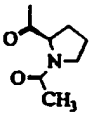
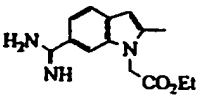
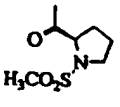
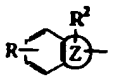
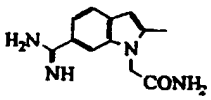
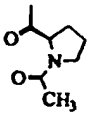
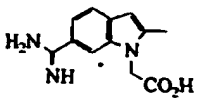
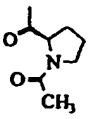
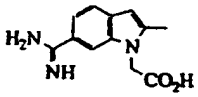
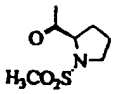
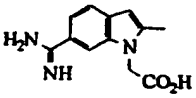
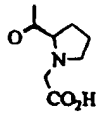
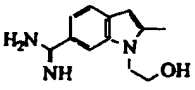
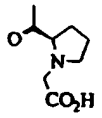
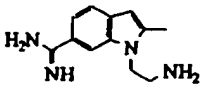
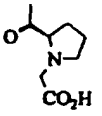
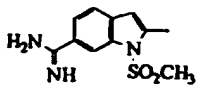
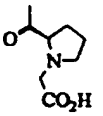
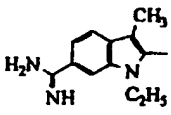
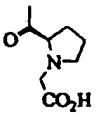
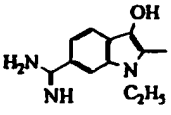
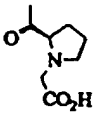
compound No.		A	R^3	n	W - Y
215		CH_2CH_2	H	2	
216		CH_2CH_2	H	2	
217		CH_2CH_2	H	2	
218		CH_2CH_2	H	2	
219		CH_2CH_2	H	2	
220		CH_2CH_2	H	1	
221		CH_2CH_2	H	1	
222		CH_2CH_2	H	1	
223		CH_2CH_2	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
224		CH_2CH_2	H	1	
225		CH_2CH_2	H	1	
226		CH_2CH_2	H	1	
227		CH_2CH_2	H	1	
228		CH_2CH_2	H	1	
229		CH_2CH_2	H	1	
230		CH_2CH_2	H	1	
231		CH_2CH_2	H	1	
232		CH_2CH_2	H	1	

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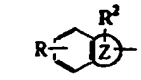
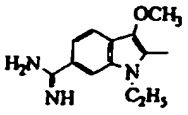
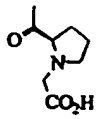
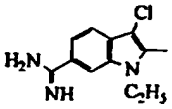
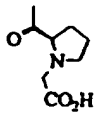
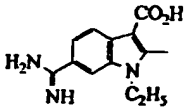
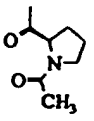
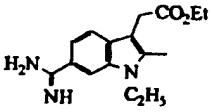
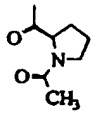
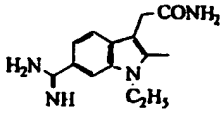
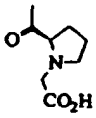
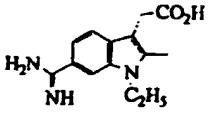
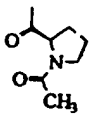
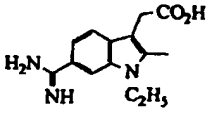
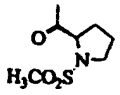
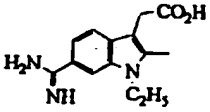
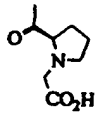
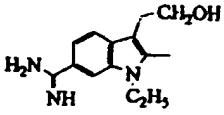
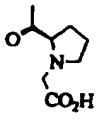
compound No.		A	R^3	n	W - Y
233		CH_2CH_2	H	1	
234		CH_2CH_2	H	1	
235		CH_2CH_2	H	1	
236		CH_2CH_2	H	1	
237		CH_2CH_2	H	1	
238		CH_2CH_2	H	1	
239		CH_2CH_2	H	1	
240		CH_2CH_2	H	1	
241		CH_2CH_2	H	1	

Table 1. (continued)

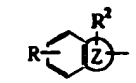
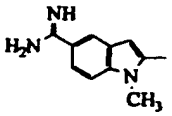
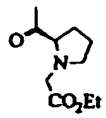
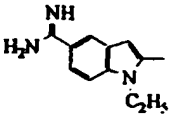
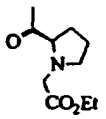
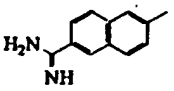
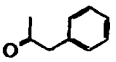
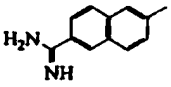
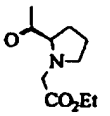
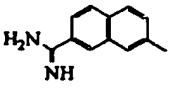
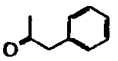
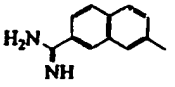
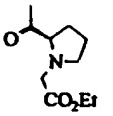
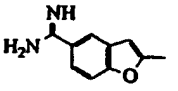
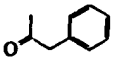
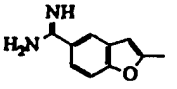
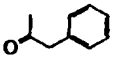
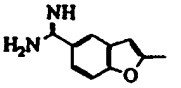
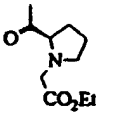
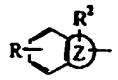
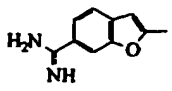
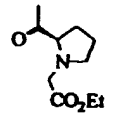
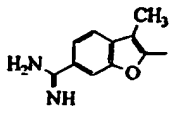
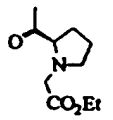
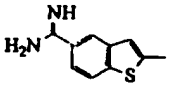
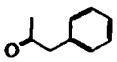
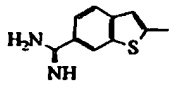
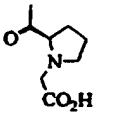
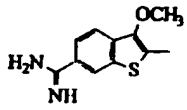
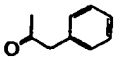
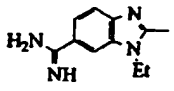
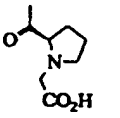
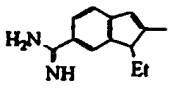
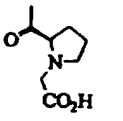
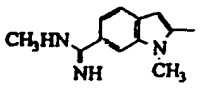
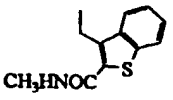
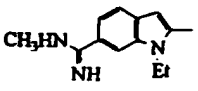
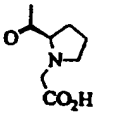
compound No.		A	R^3	n	W - Y
242		CH_2CH_2	H	1	
243		CH_2CH_2	H	1	
244		CH_2CH_2	H	1	
245		CH_2CH_2	H	1	
246		CH_2CH_2	H	1	
247		CH_2CH_2	H	1	
248		CH_2CH_2	H	1	
249		HC·CH	H	1	
250		CH_2CH_2	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
251		CH_2CH_2	H	1	
252		CH_2CH_2	H	1	
253		CH_2CH_2	H	1	
254		CH_2CH_2	H	1	
255		CH_2CH_2	H	1	
256		CH_2CH_2	H	1	
257		CH_2CH_2	H	1	
258		CH_2CH_2	H	1	
259		CH_2CH_2	H	1	

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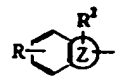
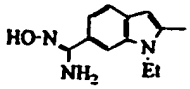
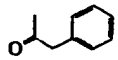
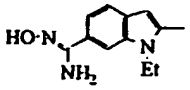
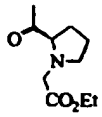
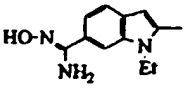
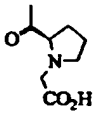
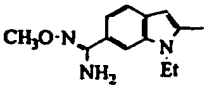
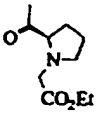
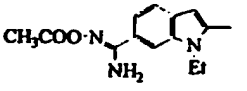
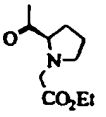
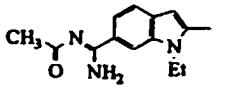
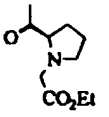
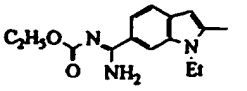
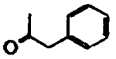
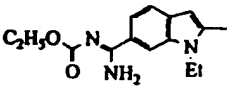
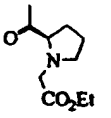
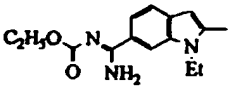
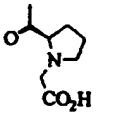
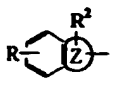
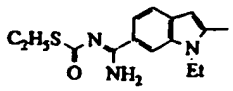
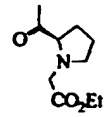
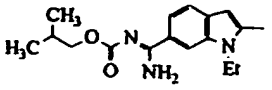
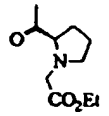
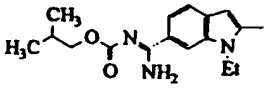
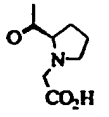
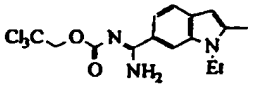
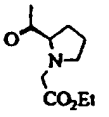
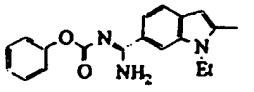
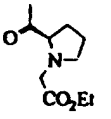
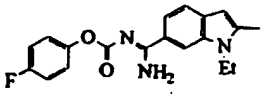
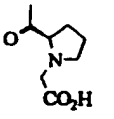
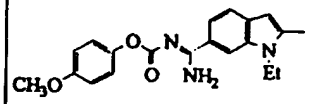
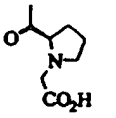
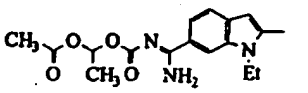
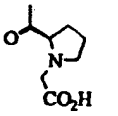
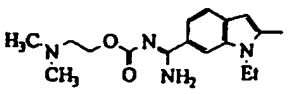
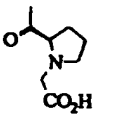
compound No.		A	R^3	n	W - Y
260		CH_2CH_2	H	1	
261		CH_2CH_2	H	1	
262		CH_2CH_2	H	1	
263		CH_2CH_2	H	1	
264		CH_2CH_2	H	1	
265		CH_2CH_2	H	1	
266		CH_2CH_2	H	1	
267		CH_2CH_2	H	1	
268		CH_2CH_2	H	1	

Table 1. (continued)

compound No.		A	R^3	n	W - Y
269		CH_2CH_2	H	1	
270		CH_2CH_2	H	1	
271		CH_2CH_2	H	1	
272		CH_2CH_2	H	1	
273		CH_2CH_2	H	1	
274		CH_2CH_2	H	1	
275		CH_2CH_2	H	1	
276		CH_2CH_2	H	1	
277		CH_2CH_2	H	1	

Specific examples of the paticularly preferred compound of formula (I) according to the present invention are as follows:

3-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]-benzo[b]thiophene-2-carboxamide,

3-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]-benzo[b]thiophene-2-carboxamide,

1-ethyl-2-[2-[(S)-1-[2-(3-chlorophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoeth-yl]benzoic acid,

1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfonylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate,

1-ethyl-2-[2-[(S)-1-[(R)-2-(carbamoylmethylamino)-2-phenylacetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetic acid,

1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate,

1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[2-[cyclopropyl(methylsulfonyl)amino]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate,

ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate,

2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl

-2-oxoethyl]cyclopropylamino]acetic acid,
ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopropylamino-4-oxobutanoate,
4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine,
ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate,
ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]acetate,
2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]acetic acid,
2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methyl-pyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid,
ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]propionate,
ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]butanoate,
ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-2-phenylacetate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[(N-cyclopropylcarbamoyl)methyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl (S)-2-[2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetylamino]propanoate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-hydroxybutanoic acid,
1-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid,
1-ethyl-2-[2-[(S)-1-[[1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrro-lidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]butanoate,

4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]butanoic acid,

ethyl 5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]pentanoate,

5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]pentanoic acid,

ethyl 6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]hexanoate,

6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]hexanoic acid,

1-ethyl-2-[2-[(S)-1-[[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-aminopropanoyl)pyrrolidin-2-yl]carbo-nyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyr-rolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoate,

1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-carbamoylpropanoyl)pyrroli-din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoic acid,

1-ethyl-2-[2-[((S)-1-[[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidn-2-yl]-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrro-

lidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)-amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]-(S)-2-[(methanesulfonyl)amino]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(4-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[(2-piperidinyl)carbonyl]pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-methyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 3-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-3-oxo-propanoate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-carbamoylacetyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-4-oxobutanoate,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]

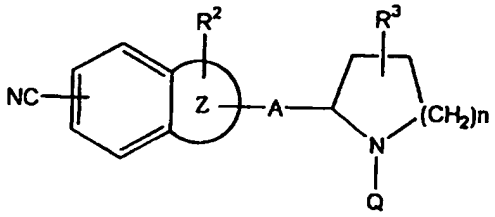
-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[((R)-1-prop-2-enoylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)-5-oxopyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
methyl-2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]piperidinyl]acetate,
1-ethyl-2-[2-[(S)-1-[(3-piperidinyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate,
ethyl 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate,
2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-1-(carbamoylmethyl)indole-6-carboxamidine, and
6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamidine.

The compound of formula (I) according to the present invention can form its pharmaceutcially acceptable salt. Such pharmaceutically acceptable salts include acid addition salts produced by acid containing pharmaceutically acceptable anion which can form a non-toxic salt, for example, an inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydroiodic acid, etc., an organic carbonic acid such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid or trifluoroacetc acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid, etc., or sulfonic acid such as methansulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, etc.

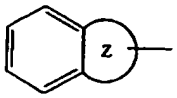
The purpose of the present invention is also to provide a process for preparation of the compound of formula (I).

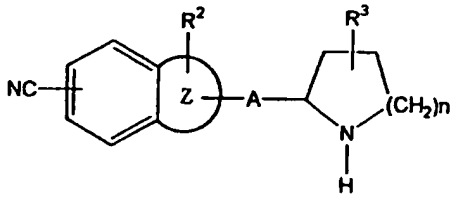
According to the method of the present invention, the compound of formula (I) and its salts can be prepared by a process wherein:

(a) an amino-protecting group of a compound of formula (V):

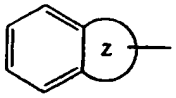


(V)

wherein  , R^2, R^3, A and n are defined as in formula (I) and Q represents an amino-protecting group, is removed to obtain a compound of formula (IV):



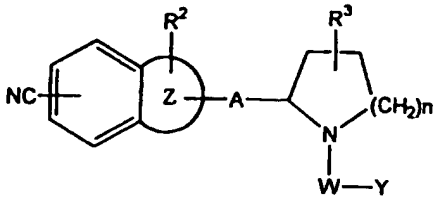
(IV)

wherein  , R^2, R^3, A and n are defined as in formula (I);

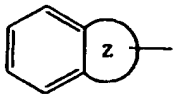
(b) the nitrile compound of formula (IV) thereby obtained is reacted with a compound of formula (VI):

Y—W——D (VI)

wherein Y and W are defined as in formula (I) and D represents hydroxy or halogen, to obtain a compound of formula (III):



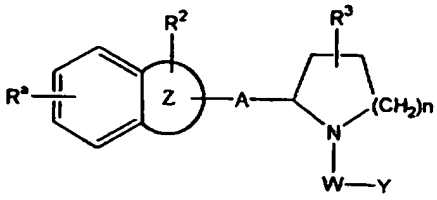
(III)

wherein  , R^2, R^3, A, Y, W and n are defined as in formula (I);

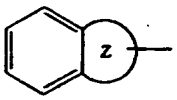
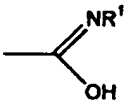
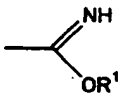
(c) the compound of formula (III) is reacted with an alcohol compound of formula (VII):

$$R^1OH \qquad \text{(VII)}$$

wherein R^1 is defined as in formula (I), in the presence of a hydrogen halide to obtain a compound of formula (II):



(II)

wherein  , R^2, R^3, A, Y, W and n are defined as in formula (I) and R^a is a group of formula  or 

wherein R^1 is defined as in formula (I); and

(d) the compound of formula (II) is reacted with ammonia.

According to the method of the present invention, in step (a) the amino-protecting group Q is removed from the compound of formula (V) to produce the compound of formula (IV).

In the compound of formula (V), a suitable amino-protecting group includes conventional groups for protecting amino radical, particularly, acyl such as carbamoyl, aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl substituted with aromatic group or heterocyclic group which are derived from carboxylic, carbonic, sulfonic and carbamic acids. For example, lower alkanoyl, lower alkylsulfonyl, carbamoyl, N-alkyl-carbamoyl, lower alkoxycarbonyl, lower alkenyloxycarbonyl, alkenoyl, aroyl, arenesulfonyl, aralkanoyl, aralkoxycarbonyl, aryloxyalkanoyl, etc. may be mentioned. Particularly preferred amino-protecting group is t-butoxycarbonyl or benzyloxycarbonyl.

The reaction for removing amino-protecting group of step (a) can be carried out by a conventional method, for example, hydrolysis in the presence of an acid (e.g. an organic acid such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid or an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, etc.) or a base (e.g. a hydroxide, hydride, carbonate or bicarbonate of alkali metal or alkaline earth metal such as sodium hydroxide, potassium hydroxide, sodium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, etc.), reduction by using a combination of a metal (e.g. zinc) or a chrome compound (e.g. chromous chloride) and an organic or inorganic acid (e.g. acetic acid, propionic acid, sulfuric acid, phosphoric acid, etc.) or by using hydrogen in the presence of a catalyst (e.g. a metallic catalyst such as palladium, platinum, nickel, etc.), and the like.

In any case, the reaction can generally be carried out in the presence of a solvent which does not adversely influence the reaction. Examples of the solvent which can preferably be used include water, dichloromethane, alcohols such as methanol, ethanol, etc., tetrahydro-furan, 1,4-dioxane, acetone, or a mixture thereof. The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating, preferably at 0℃ to 30℃.

In the reaction of step (b), the nitrile compound (IV) produced in step (a) is reacted with the compound of formula (VI) to produce the

compound of formula (III). The reaction of the compound of formula (IV) with the compound of formula (VI) can preferably carried out in the presence of a raction-inert solvent. The solvent which can preferably be used for this purpose includes acetone, 1,4-dioxane, acetonitrile, chloroform, dichloromethane, hexamethylphosphoramide, dichloroethane, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, N,N-dimethylformamide, pyridine, or a mixture thereof.

If necessary, the reaction of step (b) can be carried out in the presence of an acid acceptor. The acid acceptor which can preferably be used for this purpose includes an inorganic base, for example, hydroxide, carbonate or bicarbonate of an alkali metal or an alkaline earth metal such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, etc. or an organic base, for example, triethylamine, trimethylamine, pyridine, N,N-diisopropylethylamine, etc. Particularly, triethylamine or N,N-diisoproyl-ethylamine is most preferably used as the acid acceptor.

The reaction of step (b) can, if appropriate, be carried out in the presence of a condensing agent. The condensing agent which can preferably be used includes a carbodiimide compound such as N,N-diethylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N,N-dicyclohexylcarbodiimide, etc.

Although the reaction temperature and time are not critical, the reaction is usually carried out under from cooling to heating for 2 to 24 hours, preferably at 0℃ to 70℃ for 4 to 15 hours.

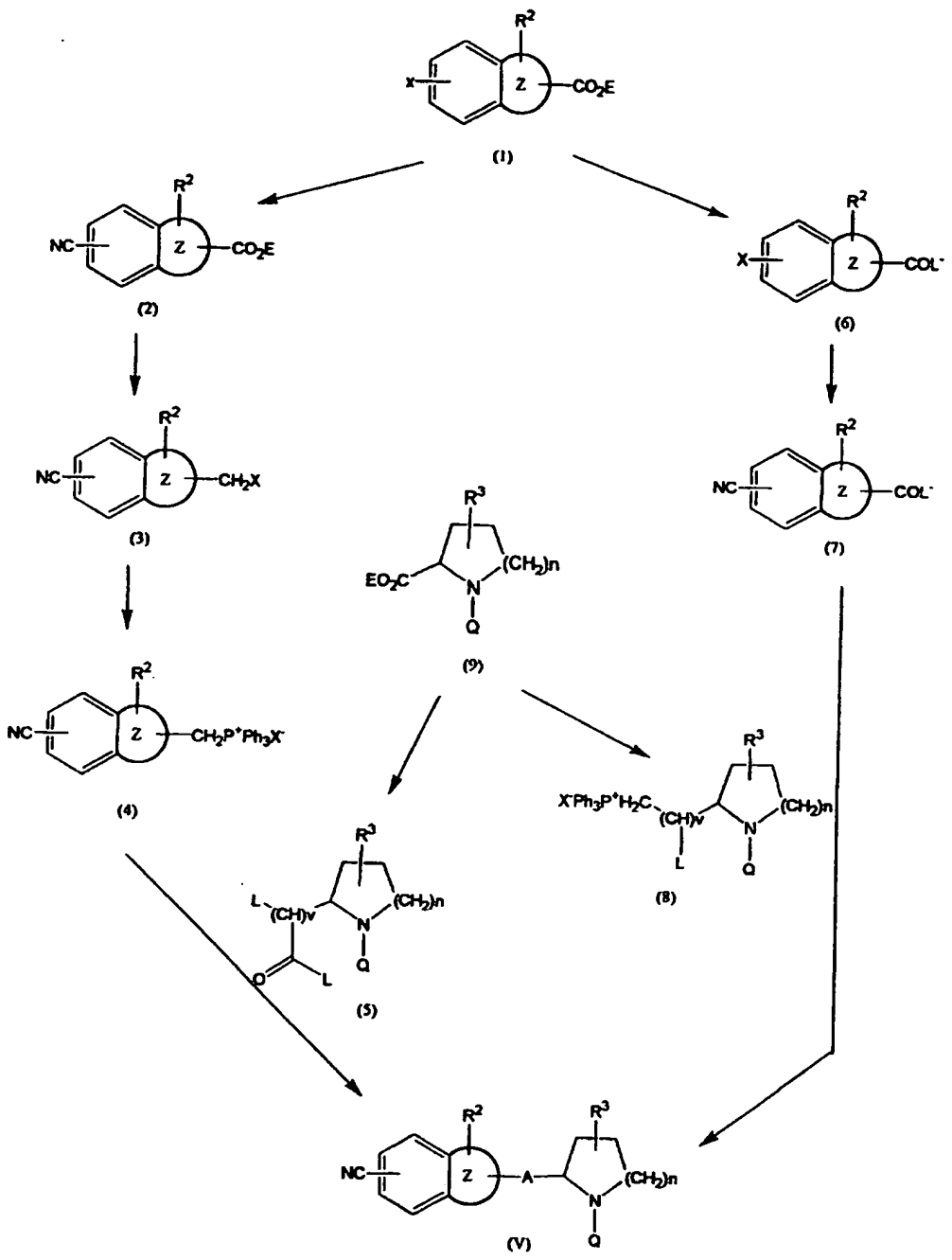
Thereafter, in step (c), the compound of formula (III) produced in step (b) is reacted with the alcohol compound of formula (VII) in the presence of hydrogen halide to produce the compound of formula (II). In this reaction, hydrogen chloride, hydrogen bromide, etc. can be used as hydrogen halide, with hydrogen chloride (HCl) being particularly preferably used. In this reaction, when the alcohol compound of formula (VII) is employed in an excessive amount, it can also be used as a

solvent. If appropriate, this reaction may also be carried out in the presence of a reaction-inert solvent such as chloroform, dichloromethane, benzene, diethyl ether, etc. Although the reaction temperature and time are not critical, the reaction is usually carried out under from cooling to heating for 2 to 48 hours, preferably at 0℃ to 30℃ for 12 to 24 hours.

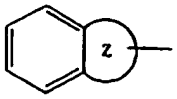
In step (d), the compound of formula (III) produced in step (c) is reacted with ammonia to produce the desired compound of formula (I). This reaction is usually carried out in a solvent, for example, C_1-C_4 alcohol such as ethanol, propanol, etc., aliphatic ether such as diethyl ether, etc., halogenated hydrocarbon such as chloroform, etc., aprotic solvent such as benzene, etc., N,N-dimethylformamide, dimethylsulfoxide, etc., or a mixture thereof. Particularly, C_1-C_4 alcohol solvent such as ethanol is preferably used. Although the reaction temperature and time in this reaction are not critical, the reaction of step (d) is usually carried out under from cooling to heating for 2 to 72 hours, preferably at 0℃ to 30℃ for 20 to 40 hours.

The compound of formula (I) prepared by the above method according to the present invention can be converted into a salt as mentioned above according to a conventional manner. The compound of formua (I) and its salts thereby produced can be separated and purified by a conventional work-up procedure, for example, column chromatography, recrystallization, etc.

All the compound of formula (V) used as the starting material and the compounds of formulas (II), (III) and (IV) produced as the intermediates in the method for preparation of the compound of formula (I) according to the present invention are novel compounds and therefore, encompassed within the scope of the present invention. The compound of formula (V) used as the starting material in the method of the present invention can be prepared by the two method as shown in the following reaction scheme.



In the above reaction scheme,



, A, R^2, R^3 and n are defined as in formual (I);

L represents hydrogen, alkyl, alkoxycarbonyl or alkoxycarbonylalkyl and in formula (5) two L groups may be same or different;
E represents hydrogen or lower alkyl;
Q represents an amino-protecting group;
X represents halogen; and
v denotes an integer of 0 to 2.

The present invention also relates to a thrombin inhibitor composition which contains as an active component a therapeutically effective amount of the compound of formula (I) or its pharmaceutically acceptable salt together with pharmaceutically acceptable carriers. The composition of the present invention exhibits potent thrombin inhibitory activity and can therefore be used as an agent for prevention and treatment of thrombosis.

The compound of formula (I) according to the present invention is preferable since it is effective even when orally administered.

For clinical purposes, an effective daily dosage of the compound according to the present invention may generally be in the range of 0.1 to 30㎎ per ㎏ of body weight, and preferably in the range of 0.5 to 10㎎ per ㎏ of body weight. A dosage suitable for an individual subject can appropriately be determined by a specialist depending on a kind of the compound of formula (I) to be applied, weight, sex, health and nutritional condition of the patient, time and method of administration, excretion rates, a kind of medicines to be administered in combination with the compound of formula (I) and severity of disease.

The compound of the present invention may be administered either orally or by injection, depending on the dosage and the therapeutic effect desired.

Orally administrable solid preparations may be in the form of capsules, tablets, pills, powders and granules, with capsule and tablet preparations being preferable. The tablets and pills can preferably be

applied to enteric coating. The solid dosage form can be prepared by intimately mixing the compound of formula (I) according to the present invention with carriers, for example, one or more inert diluents such as sucrose, lactose, starch, etc., lubricants such as magnesium stearate, disintegrating agents, binders, etc.

As mentioned above, the compositions containing the compound of formula (I) according to the present invention are characterized by their superior effect even when orally administered. These has been demonstrated through pharmacokinetic experiments using rats and dogs as the test animals, in which the active compound is shown to be retained in blood for a long time when the composition is orally administered. The compound of the present invention is, therefore, more useful than thrombin inhibitors disclosed in the prior art because it can be effectively used in the form of an oral preparation.

The composition containing the compound of formula (I) according to the present invention can also be formulated in the form of an injectable preparation, for example, as a sterilized injectable aqueous or oily suspension using suitable dispersing agents, wetting agents or suspending agents. Aqueous solvents which can be used for this purpose include water, Ringer's solution or isotonic NaCl solution. Sterilized fixing oils may also be used as a solvent or suspending agent. Non-irritable fixing oils including mono-, di-glycerides can be used for this purpose, and fatty acids such as oleic acid may be used in injectable preparations.

In addition, according to the results of experiment, it has been identified that the compound of formula (I) according to the present invention exhibits potent thrombin inhibitory activity without acute toxicity in mammals, such as rats and dogs.

Although the present invention is specifically illustrated by the following examples, the present invention is not in any manner limited by these examples.

Example 1 : Synthesis of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-carbonitrile (Compound 1)

a) Synthesis of 4-methyl-3-nitrobenzenecarbonitrile:

In a 250㎖ flask, 10g of 4-methylbenzenecarbonitrile was dissolved in 30㎖ of concentrated sulfuric acid and then cooled to 0℃. 7㎖ of nitric acid mixed with 10㎖ of concentrated sulfuric acid was slowly added thereto over one hour at -2℃ to 0℃. The reaction solution was poured into ice water and then stirred. The resulting precipitate was filtered, washed three times with water and then dried. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 11.2g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.30(s, 1H), 7.80(d, 1H), 7.53(d, 1H), 2.7(s, 3H)

b) Synthesis of ethyl 3-(4-cyano-2-nitrophenyl)-2-sodiumprop-2-enoate:

To a 500㎖ flask, 2.51g of sodium and 60㎖ of tetrahydrofuran were added and 30㎖ of ethanol was then added thereto. The mixture was stirred at room temperature until sodium was completely dissolved. A solution of 14.8㎖ of diethyl oxalate in tetrahydrofuran was slowly added thereto and the mixture was stirred for 10 minutes at room temperature. 16g of 4-methyl-3-nitrobenzenecarbonitrile dissolved in tetrahydrofuran was added thereto and the mixture was stirred for 18 hours at room temperature. The reaction solution was evaporated and ether was added to the residue. The resulting precipitate was filtered, washed three times with ether and then dried to obtain 26.4g of the title compound as a brown solid.

c) Synthesis of ethyl 6-cyanoindole-2-carboxylate:

26g of ethyl 3-(4-cyano-2-nitrophenyl)-2-sodiumprop-2-enoate

and 59.8g of Zn were introduced into a 500㎖ flask and 200㎖ of acetic acid was added thereto. The mixture was stirred for 2 hours at room temperature and then for 4 hours at 60~70℃. The reaction solution was evaporated, and the residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 4.16g of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.82(m, 2H), 7.42(d, 1H), 7.29(s, 1H), 4.49(m, 2H), 1.47(t, 3H)

d) Synthesis of ethyl 6-cyano-1-ethylindole-2-carboxylate:

In a 1ℓ flask, 23.5g of ethyl 6-cyanoindole-2-carboxylate was dissolved in 300㎖ of dimethylformamide, and 6.6g of 60% NaH was slowly added thereto at 0℃. 17.6㎖ of iodoethane was then added thereto at -10~0℃ and the mixture was stirred for 2 hours at room temperature. The reaction solution was cooled and, after adding ice, diluted with water and then extracted three times with ethyl acetate. The organic extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acteate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 26.2g of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.77(m, 2H), 7.34(m, 2H), 4.64(m, 2H), 4.42(m, 2H), 1.43(m, 6H)

e) Synthesis of 1-ethyl-2-(hydroxymethyl)indole-6-carbonitrile:

In a 1ℓ flask, 26.27g of ethyl 6-cyano-1-ethylindole-2-carboxylate and 0.91g of sodium bicarbonate were dissolved with 300㎖ of tetrahydrofuran and then cooled to 0℃. To this mixture was added $CaI_2 \cdot H_2O$ and then slowly added $NaBH_4$. The reaction mixture was stirred while slowly warming from 0℃ to room temperature with stirring.

After examined by TLC, ice and a catalytic amount of acetic acid were added thereto at 0℃ and the mixture was stirred. The reaction solution was evaporated to remove tetrahydrofuran, and the residue was diluted with water and extracted three times with ethyl acetate. The organic extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and then evaporated to obtain 18.2g of the title compound as a white solid.

^1H NMR($CDCl_3$, ppm) : δ 7.63(m, 2H), 7.26(m, 1H), 6.43(s, 1H), 4.83(s, 2H), 4.29(m, 2H), 1.41(t, 3H)

f) Synthesis of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide:

In a 500㎖ flask, 18.2g of 1-ethyl-2-(hydroxymethyl)indole-6-carbonitrile was dissolved in 200㎖ of dichloromethane and then cooled to 0℃. 3.45㎖ of PBr_3 was slowly added thereto, and the mixture was stirred for 4 hours at room temperature. dichloromethane was then added and the reaction mixture was washed with aqueous Na_2CO_3 solution, diluted with water and then extracted three times with dichloromethane. The organic extracts were combined, dried over $MgSO_4$ and then evaporated to obtain 6-cyano-1-ethyl-2-bromomethyl indole. The resulting product was dissolved in 200㎖ of toluene and 30.9g of triphenylphosphine was added thereto. The mixture was stirred for 10 hours at refluxing temperature and then cooled to room temperature. To this reaction solution was added diethyl ether, and the resulting precipitate was then filtered, washed several times with diethyl ether and dried to obtain 29g of the title compound as a pale brown solid.

g) Synthesis of (S)-methyl pyrrolidine-2-carboxylate:

In a 250㎖ flask, 10g of L-proline was dissolved in 150㎖ of methanol, and HCl gas was bubbled therein at 0℃ for 2 hours to saturate

the solution. The reaction solution was then stirred for 5 hours at room temperature and evaporated to remove the solvent, thereby obtain 11.2g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 4.50(m, 1H), 3.86(s, 3H), 3.52(m, 2H), 2.48(m, 1H), 2.20(m, 3H)
MS : 130(M+1)$^+$, 116

h) Synthesis of 1-tert-butyl-(S)-2-(methoxycarbonyl)pyrrolidine carboxylate:

In a 500㎖ flask, 11.2g of (S)-methyl pyrrolidine-2-carboxylate was dissolved in 200㎖ of dichloromethane and 12㎖ of triethylamine was added, and the mixture was then stirred for 5 minutes. 20.9g of $(Boc)_2O$ dissolved in dichloromethane was added thereto at 0℃, and the reaction mixture was stirred for 4 hours at room temperature, diluted with water and extracted three times with dichloromethane. The organic extracts were combined, dried over $MgSO_4$ and then evaporated to obtain 19.9g of the title compound as a colorless oil.

^{1}H NMR(MeOH-d_4, ppm) : δ 4.20(m, 1H), 3.68(s, 3H), 3.37(m, 2H), 2.22 (m, 1H), 1.89(m, 3H), 1.41(m, 9H)

i) Synthesis of 1-tert-butyl-(S)-2-formylpyrrolidine carboxylate:

In a 500㎖ flask, 9.8g of 1-tert-butyl-(S)-2-(methoxycarbonyl)-pyrrolidine carboxylate was dissolved in 200㎖ of toluene and 85.5㎖ of DIBAL-H(diisobutylaluminum hydride, 1.0M in toluene) was slowly added over 1.5 hour while cooling to -78℃. 15㎖ of methanol was then added thereto, and the mixture was stirred for 30 minutes at room temperature. To this solution, aqueous solution of Rochell's salt (potassium sodium tartrate tetrahydrate) was added, and the reaction solution was stirred for about one hour at room temperature and then extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$ and evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions

containing the desired product were combined and then evaporated to obtain 8g of the title compound as a colorless oil.

j) Synthesis of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-pyrrolidine carboxylate:

In a 500mℓ flask, 17.4g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 6.6g of 1-tert-butyl-(S)-2-formylpyrrolidine carboxylate were dissolved in a mixed solvent of tetrahydrofuran/ethanol (1:1), and 6.4mℓ of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. The reaction solution was stirred for 15 hours at room temperature and evaporated to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 7.8g of the title compound as a yellow oil.

k) Synthesis of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidine carboxylate:

In a 500mℓ flask, 13g of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethyl-indol-2-yl)vinyl]pyrrolidine carboxylate was dissolved in 250mℓ of ethanol, and 4g of 10% palladium on activated carbon was slowly added thereto. Hydrogen gas was bubbled into the reaction solution and the mixture was stirred for 3 hours at room temperature. The reaction solution was filtered through a celite and evaporated to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 12g of the title compound as a brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60(m, 2H), 7.28(m, 1H), 6.36(s, 1H), 4.15(m, 2H), 3.94(m, 1H), 3.72(m, 1H), 3.38(m, 3H), 2.76(t, 2H), 1.46(s, H), 1.39(m, 3H)

l) Synthesis of 1-ethyl-2-[2-((S)-pyrrolidin-2-yl)ethyl]indole-6-carbonitrile (Compound I-a):

In a 250㎖ flask, 3.7g of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethyl-indol-2-yl)ethyl]pyrrolidine carboxylate was dissolved in 100㎖ of dichloromethane, and 18.2㎖ of trifluoroacetic acid was slowly added thereto at 0℃. The reaction mixture was stirred for about 2 hours at room temperature, and after adding dichloromethane, then diluted with water and washed three times with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted three times with dichloromethane. The organic extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(3:1)]. The fractions containing the desired product were combined and then evaporated to obtain 2.2g of the title compound as a pale yellow foam.

^1H NMR($CDCl_3$, ppm) : δ 7.48(m, 2H), 7.28(m, 1H), 6.33(s, 1H), 4.03(m, 2H), 3.58(m, 1H), 3.27(m, 2H), 2.85(m, 2H), 2.35(m, 1H), 2.11(m, 3H), 2.00(m, 1H), 1.80(m, 1H), 1.27(t, 3H)

m) Synthesis of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-carbonitrile:

66㎎ of the compound I-a obtained in the above l) was dissolved in dichloromethane and then cooled to 0℃. To this solution, 46㎕ of triethylamine was added and 38㎕ of benzyl chloride was then slowly added. The reaction mixture was stirred for 4 hours at room temperature and then diluted with excess of dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and filtered under reduced pressure. The filtrate was concentrated and the concentrate was purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)]. The fractions containing the desired product were combined and evaporated to obtain 39㎎ of the title compound.

n) Synthesis of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-carboxamidine:

39㎎ of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-

carbonitrile was dissolved in ethanol and cooled to 0℃. HCl gas was bubbled for 45 minutes into the solution, and the reaction solution was stirred at room temperature overnight and concentrated under reduced pressure to remove the solvent. The residue was dissolved in ethanol and ammonia gas was bubbled into the solution for one hour at 0℃. The reaction solution was stirred overnight at room temperature and then distilled under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(4:1)] on NH-DM1020 silica to obtain 32㎎ of the title compound a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.93(s, 1H), 7.66(d, 1H, J=8.41Hz), 7.44(d, 1II, J=8.41Hz), 7.34-7.27(m, 5H), 6.40(s, 1H), 4.28(q, 2H), 4.07(d, 1H), 2.95-2.88(m, 3H), 2.60(m, 1H), 2.31-1.90(m, 4H), 1.80-1.55 (m, 5H), 1.40(t, 3H, J=7.21Hz)

Example 2 : Synthesis of ethyl 2-[(S)-2-[2-(6-amidino-1-methyl-indol-2-yl)ethyl]pyrrolidinyl]-2-phenylacetate (Compound 2)

a) Synthesis of 6-cyano-1-methylindole-2-methyl triphenyl phosphonium bromide:

The reaction was carried out according to the same procedure as Examples 1-a) through 1-f), except that iodomethane was used in place of iodoethane in Example 1-d), to obtain 15g of the title compound as a pale brown solid.

^{1}H NMR(DMSO-d_6, ppm) : δ 8.00(s, 1H), 7.92(m, 3H), 7.84-7.68(m, 12H), 7.62(d, 1H, J=8.24Hz), 7.35(d, 1H, J=8.24Hz), 6.28(s, 1H), 5.57(d, 2H, J=15.2Hz), 3.19(s, 3H)

b) Synthesis of 1-methyl-2-[2-((S)-pyrrolidin-2-yl)ethyl]-indole-6-carbo -nitrile (Compound I-b):

6-Cyano-1-methylindole-2-methyl triphenylphosphonium bromide obtained in the above a) was reacted according to the same procedure as Example 1-l) to obtain 6.4g of the title compound as a pale yellow foam.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.83(s, 1H), 7.62(d, 1H, J=8.24Hz), 7.30(d, 1H, J=8.24Hz), 6.47(s, 1H), 3.80(s, 3H), 3.64(m, 1H), 3.32(m, 2H), 3.00(m, 2H), 2.41-1.98(m, 5H), 1.80(m, 1H)

c) Synthesis of ethyl 2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]-pyrrolidinyl]-2-phenylacetate:

90㎎ of the compound I-b obtained in the above b) and 86㎎ of ethyl-2-bromo-2-phenylacetate were treated according to the same procedure as Example 1-m) to obtain 85㎎ of the title compound as a pale yellow solid.

d) Synthesis of ethyl 2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]-pyrrolidinyl]-2-phenylacetate:

81㎎ of ethyl 2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]-pyrrolidinyl]-2-phenylacetate obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 19㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.82(d, 1H, J=11.06Hz), 7.52(d, 1H, J=8.1Hz), 7.32(m, 3H), 7.19(m, 3H), 6.10(s, 1H), 4.36(s, 1H), 4.00(m, 2H), 1.95(m, 2H), 1.74-1.45(m, 6H), 1.06(m, 3H)

Example 3 : Synthesis of 2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-phenylacetic acid (Compound 3)

13㎎ of ethyl 2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]-pyrrolidinyl]-2-phenylacetate obtained in Example 2 was dissolved in 5㎖ of 35% hydrochloric acid solution, and the resulting solution was heated to 60℃ and stirred for 1.5 hours, and then stirred at room temperature overnight. The reaction solvent was removed by distillation under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(2:3)] on NH-DM1020 silica. The fractions containing the desired product were combined and then distilled under reduced pressure to obtain 6.2㎎ of the title compound as a

pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.75(s, 1H), 7.59-7.51(m, 1H), 7.31-7.20(m, 5H), 6.33(s, 1H), 4.13(s, 1H), 3.74(s, 3H), 3.61(s, 1H), 2.98(m, 2H), 2.89(m, 3H), 2.75(m, 2H), 2.40(m, 1H), 2.35-2.05(m, 3H), 1.80-1.77(m, 6H)

Example 4 : Synthesis of 1-methyl-2-[2-[(S)-1-(1-naphthylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 4)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(1-naphthylmethyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

89㎎ of the compound I-b obtained in Example 2-b), 127㎎ of 1-naphthalenemethanol and 148㎎ of triphenylphosphine were dissolved in chloroform, and 104㎕ of DEAD(diethylazodicarboxylate) was slowly added thereto while stirring at room temperature. The mixture was stirred at room temperature overnight and distilled under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)]. The fraction containing the desired product was distilled under reduced pressure to obtain 33㎎ of the title compound.

b) Synthesis of 1-methyl-2-[2-[(S)-1-(1-naphthylmethyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamide:

30㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 11㎎ of the title compound as a yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.20(m, 1H), 7.76(m, 2H), 7.68(d, 1H, J=8.66Hz), 7.52(d, 1H, J=8.21Hz), 7.37-7.22(m, 5H), 6.21(s, 1H), 4.37(d, 1H), 3.65(m, 1H), 3.55(m, 1H), 2.10-1.90(m, 5H), 1.66-1.61 (m, 6H)

Example 5 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 5)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylmethyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile:

In a 25mℓ flask, 70mg of the compound I-b obtained in Example 2-b) and 54mg of 2-naphthalenemethanol were dissolved in 5mℓ of tetrahydrofuran. To the resulting solution, 105mg of triphenylphosphine was added and 0.08mℓ of DEAD was then added at room temperature. The mixture was stirred for about 40 hours at room temperature and then evaporated to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/methanol(10:1)]. The fractions containing the desired product were combined and then evaporated to obtain 20mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(m, 1H), 7.69(m, 4H), 7.52(m, 1H), 7.47 (m, 3H), 7.28(d, 1H), 6.30(s, 1H), 4.14(d, 1H), 3.60(s, 3H), 3.57(d, 1H), 2.99(m, 1H), 2.88(m, 1H), 2.76(m, 1H), 2.63(m, 1H), 2.40(m, 1H), 2.14(m, 2H), 1.79(m, 4H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylmethyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine:

18mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 10mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4. ppm) : δ 7.76-7.62(m, 5H), 7.51(d, 1H), 7.35(m, 4H), 6.24(s, 1H), 4.06(d, 1H), 3.60(s, 3H), 3.45(d, 1H), 2.86(m, 1H), 2.72(m, 2H), 2.53(m, 1H), 2.27(m, 1H), 2.04(m, 2H), 1.69(m, 4H)

Example 6 : Synthesis of 1-methyl-2-[2-[(S)-1-(benzo[d]1,3-dioxolen-5-yl-methyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 6)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(benzo[d]1,3-dioxolen-5-ylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

In a 100㎖ flask, 100㎎ of the compound I-b obtained in Example 2-b) and 66㎎ of piperonyl alcohol were reacted according to the same procedure as Example 5-a) to obtain 40㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.31(d, 1H), 6.83(s, 1H), 6.72(m, 2H), 6.32(d, 1H), 5.91(s, 2H), 3.92(d, 1H), 3.69(s, 3H), 3.21(d, 1H), 2.98(m, 1H), 2.86-2.74(m, 2H), 2.54(m, 1H), 2.19(m, 1H), 2.03(m, 2H), 1.77(m, 3H), 1.73(m, 1H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(benzo[d]1,3-dioxolen-5-ylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

40㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 16㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.89(m, 1H), 7.39(m, 2H), 6.79(s, 1H), 6.69(m, 2H), 6.14(s, 1H), 5.89(s, 2H), 3.88(d, 1H), 3.57(s, 3H), 3.11(d, 1H), 2.91(m, 1H), 2.71-2.58(m, 2H), 2.45(m, 1H), 2.09(m, 1H), 1.98(m, 2H), 1.68(m, 3H), 1.54(m, 1H)

MS : 405$(M+1)^+$, 271, 202, 135

Example 7 : Synthesis of methyl 3-[[(S)-2-[2-(6-amidino-1-methyl-indol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carbo-xylate (Compound 7)

a) Synthesis of methyl 3-[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]-pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxylate:

80㎎ of the compound I-b obtained in Example 2-b) was dissolved in dichloromethane and cooled to 0℃. To this solution, 59㎕ of triethyl-

amine was added and 110mg of methyl 3-bromomethylbenzo[b]thiophene-2-carboxylate was slowly added. The reaction mixture was stirred for 3.5 hours at room temperature and diluted with excess of dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and then filtered under reduced pressure. The filtrate was then concentrated. The concentrate was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)]. The fractions containing the desired product were combined and then evaporated to obtain 80mg of the title compound as a white solid.

b) Synthesis of methyl 3-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]-pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxylate:

80mg of the compound obtained in the above a) was dissolved in 5 mℓ of methanol and cooled to 0℃. HCl gas was bubbled into the solution for 50 minutes and the reaction solution was stirred at room temperature overnight and concentrated under reduced pressure to remove the solvent. The residue was dissolved in 5mℓ of methanol, and ammonia gas was bubbled for one hour at 0℃ into the solution. The reaction solution was stirred at room temperature overnight and then distilled under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(4:1)] on NH- DM1020 silica to obtain 22mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.13(d, 1H, J=8.06Hz), 7.88(s, 1H), 7.62(d, 1H, J=8.34Hz), 7.47-7.37(m, 3H), 6.30(s, 1H), 4.55(d, 1H, J=12.4Hz), 4.07(d, 1H, J=12.4Hz), 3.83(s, 3H), 3.67(s, 3H), 2.83-2.67(m, 4H), 2.26(m, 1H), 2.15-2.05(m, 2H), 1.69-1.57(m, 4H)

Example 8 : Synthesis of 3-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxamide (Compound 8)

1.46g of the compound I-a obtained in Example 1-l) was treated according to the same procedure as Example 7-a) to obtain 1.38g of the

white solid product, which was then treated according to the same procedure as Example 7-b) to obtain 930㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.95(d, 1H), 7.79(d, 1H), 7.73(m, 1H), 7.48(d, 1H), 7.33(m, 3H), 6.09(s, 1H), 4.22(d, 1H), 3.99(m, 2H), 3.92(d, 1H), 2.85(m, 1H), 2.68-2.61(m, 4H), 2.39(m, 1H), 2.15(m, 1H), 1.95(m, 1H), 1.74-1.58(m, 4H), 1.86(t, 3H)

Example 9 : Synthesis of 3-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxamide (Compound 9)

80㎎ of 3-[[(S)-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxamide was treated according to the same procedure as Example 7-b) to obtain 36㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.90(d, 1H, J=7.5Hz), 7.77(d, 1H, J=7.42Hz), 7.71(s, 1H), 7.47(d, 1H, J=8.36Hz), 7.33-7.24(m, 3H), 6.10(s, 1H), 4.19(d, 1H, J=12.99Hz), 4.14(d, 1H, J=7.58Hz), 3.49(s, 1H), 2.85 (m, 1H), 2.71-2.60(m, 3H), 2.40(m, 1H), 1.92(m, 1H), 1.73-1.58(m, 4H)

Example 10 : Synthesis of 1-methyl-2-[2-[(S)-1-[[2-(N-methylcarbamoyl)benzo[b]thiophen-3-yl]methyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 10)

a) Synthesis of N-methyl [3-[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)-ethyl]pyrrolidinyl]methyl]benzo[b]thiophen-2-yl]formamide:

Methyl 3-[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]methyl]benzo[b]thiophene-2-carboxylate was dissolved in methanol solution of 40% methylamine and then stirred for 2 hours at room temperature. The reaction solution was evaporated to obtain the residue which was then purified with silica gel column chromatography [eluent:

dichloromethane/ethyl acetate(2:1)] to obtain 70㎎ of the title compound as a white foam.

^{1}H NMR($CDCl_3$, ppm) : δ 10.64(d, 1H, J=4.83Hz), 7.88(d, 1H), 7.80(d, 1H), 7.55(d, 2H, J=8.19Hz), 7.40(m, 1H), 7.35-7.31(m, 2H), 6.22(s, 1H), 4.18(d, 1H), 3.87(d, 1H), 3.50(s, 3H), 3.02(d, 3H), 2.99(m, 1H), 2.77-2.70(m, 3H), 2.45(m, 1H), 2.13(m, 1H), 2.07(m, 1H), 1.85-1.82(m, 2H), 1.68-1.63(m, 2H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[[2-(N-methylcarbamoyl)benzo[b]-thiophen-3-yl]methyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

35㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 25㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 10.67(d, 1H, J=4.17Hz), 8.08(s, 1H), 7.81-7.76(m, 2H), 7.49-7.45(m, 2H), 7.37-7.32(m, 2H), 6.10(s, 1H), 4.04(d, 1H), 3.57(s, 3H), 2.93(d, 3H), 2.86(brs, 1H), 2.65(m, 3H), 2.33(m, 1H), 2.20-2.17(m, 1H), 2.02-1.96(m, 1H), 1.77-1.73(m, 2H), 1.58-1.54(m, 2H)

Example 11 : Synthesis of 1-methyl-2-[2-[(S)-1-[(4-methoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 11)

a) Synthesis of 1-methyl-2-[2-[(S)-1-[(4-methoxyphenyl)carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

70㎎ of the compound I-b obtained in Example 2-b) and 67㎎ of p-methoxybenzoic acid were dissolved in dichloromethane, and 119㎎ of WSCIHCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) was added thereto. The reaction mixture was stirred for 2.5 hours at room temperature, and water was added thereto. The reaction solution was extracted two times with dichloromethane. The extracts were

combined, dried over $MgSO_4$ and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/ methanol(50:1)] to obtain 78㎎ of the title compound as a white solid.

^1H NMR($CDCl_3$, ppm) : δ 7.54-7.45(m, 2H), 7.26(d, 1H), 7.20-7.13(dd, 2H), 6.90-6.80(dd, 2H), 6.39(s, 1H), 4.29-4.18(brs, 1H), 3.78(s, 3H), 3.66(s, 3H), 3.50(t, 2H), 2.79(t, 2H), 2.20-2.33(m, 1H), 1.97(m, 3H), 1.74(m, 2H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[(4-methoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

78㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 26㎎ of the title compound as a yellowish white solid.

^1H NMR(MeOH-d_4, ppm) : δ 7.76(s, 1H), 7.48(d, 1H), 7.06(d, 2H), 6.77(d, 2H), 6.33(s, 1H), 4.13-4.05(brs, 1H), 3.65(s, 3H), 3.49(s, 3H), 3.54-3.40(m, 2H), 2.82-2.75(m, 2H), 2.25-1.60(m, 6H)

Example 12 : Synthesis of 1-methyl-2-[2-[(S)-1-[(3,4-dimethoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 12)

a) Synthesis of 1-methyl-2-[2-[(S)-1-[(3,4-dimethoxyphenyl)carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

50㎎ of the compound I-b obtained in Example 2-b) and 52㎎ of 3,4-dimthoxybenzoic acid were reacted according to the same procedure as Example 11-a) to obtain 53㎎ of the title compound as a white solid.

^1H NMR(MeOH-d_4, ppm) : δ 7.77(s, 1H), 7.54(d, 1H), 7.25(d, 1H), 7.10(s, 2H), 7.00(d, 1H), 6.50(s, 1H), 4.38-4.25(brs, 1H), 3.83(s, 3H), 3.78(s, 3H), 3.65-3.50(m, 2H), 2.97-2.87(m, 2H), 2.28-1.60(m, 6H)

b) Synthesis of 1-methyl-2-[2-[(2S)-1-[(3,4-dimethoxyphenyl)carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

42㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 21㎎ of the title compound as a yellowish green solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.47-7.40(d, 1H), 7.32-7.20(m, 1H), 7.09(brs, 2H), 6.83-6.81(br, 1H), 6.34(s, 1H), 4.33(brs, 1H), 3.89(s, 3H), 3.86(s, 3H), 3.73(bs, 2H), 3.48(s, 3H), 2.79(brs, 2H), 2.22-1.60(m, 6H)

Example 13 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 13)

500㎎ of the compound I-b obtained in Example 2-b) was dissolved in 10㎖ of dichloromethane, and 460㎕ of triethylamine and 0.35 ㎖ of phenylacetyl chloride were added thereto. The reaction mixture was treated according to the same procedure as Example 1-m) to obtain 430㎎ of 1-methyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile, which was then treated according to the same procedure as Example 1-n) to obtain 267㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.92(m, 1H), 7.66(m, 1H), 7.61(m, 1H), 7.36-7.28(m, 5H), 6.46(s, 1H), 4.21(m, 1H), 3.85(s, 3H), 3.77(m, 2H), 3.60(t, 3H, J=6.60Hz), 2.84(m, 2H), 2.27(m, 1H), 1.99-1.82(m, 6H)

Example 14 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 14)

a) Synthesis of 1-ethyl-2-[2-[(2S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile:

80㎎ of the compound I-a obtained in Example 1-l) was dissolved

in dichloromethane and then cooled to 0℃. To this solution, 56㎕ of triethylamine was added and 53㎕ of phenylacetyl chloride was then slowly added. The reaction mixture was stirred for 4 hours at room temperature and then diluted with excess of dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and filtered under reduced pressure. The filtrate was concentrated. The concentrate was then purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)]. The fractions containing the desired product were combined and evaporated to obtain 81㎎ of the title compound as a pale yellow solid.

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine:

80㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 60㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(d, 1H, J=7.15Hz), 7.53(d, 1H, J=8.33 Hz), 7.30(d, 1H, J=8.33Hz), 7.22-7.13(m, 4H), 6.36(s, 1H), 4.14 (m, 3H), 3.62(d, 1H), 3.49(m, 2H), 2.73(t, 2H, J=8.13Hz), 2.15(m, 1H), 1.93-1.86(m, 5H), 1.26(t, 3H, J=7.15Hz)

Example 15 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-chlorophenyl)-acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 15)

70㎎ of the compound I-a obtained in Example 1-l) and 67㎎ of 3-chlorophenylacetic acid were treated according to the same procedure as Example 11-a) to obtain 40㎎ of the pale yellow oily product. 38㎎ of this product was then treated according to the same procedure as Example 1-n) to obtain 18㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.84(s, 1H), 7.41(d, 1H, J=8.24Hz), 7.16-7.12(m, 4H), 7.06(m, 1H), 6.27(s, 1H), 4.15-4.10(m, 3H), 3.54(s, 2H), 3.49-3.42(m, 2H), 2.70-2.65(m, 2H), 2.24-2.20(m, 1H), 1.97-1.89

(m, 3H), 1.71-1.63(m, 2H), 1.25(t, 3H, J=7.00Hz)

Example 16 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 16)

a) Synthesis of 2-[3-(1,1,2,2-tetramethyl-1-silapropoxy)phenyl]acetic acid:

1g of 3-hydroxyphenylacetic acid was dissolved in 10mℓ of N,N-dimethylformamide, and 3.97g of TBDMSCl (ter-butyl dimethylsilyl chloride) and 2.69g of imidazole were added thereto. The reaction mixture was stirred for 14 hours at room temperature and then for 4 hours at 35℃. The reaction solution was diluted with 150mℓ of dichloromethane and then washed with saturated saline and 0.7N cold HCl solution. The organic layer was washed again with saturated saline, dried over sodium sulfate and filtered. The filtrate was concentrated. The residue was then dissolved in 20mℓ of methanol and 8mℓ of tetrahydrofuran, and aqueous K_2CO_3 solution (400mg/8mℓ) was added thereto. The reaction mixture was stirred for 1.5 hours at room temperature and then concentrated. To the residue was added saturated saline and the reaction solution was acidified with 10% aqueous citric acid solution to pH 4 and extracted with dichloromethane (100mℓ×2). The organic layer was washed with saturated saline, dried over sodium sulfate and then filtred. The filtrate was concentrated. The residue was then purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)] to obtain 1.69g of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.02-6.95(m, 1H), 6.73-6.69(m, 1H), 6.59-6.53 (m, 2H), 3.40(s, 2H), 0.79(s, 9H), 0.01(s, 6H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(1,1,2,2-tetramethyl-1-silapropoxy)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

300mg of the compound obtained in the above a) was treated

according to the same procedure as Example 11-a) to obtain 170㎎ of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.42-7.36(m, 2H), 7.12-7.09(m, 1H), 7.02-6.97 (m, 1H), 6.71-6.68(m, 1H), 6.61-6.54(m, 2H), 6.23(s, 1H), 4.13 (brs, 1H), 3.95(q, 2H), 3.45(s, 2H), 3.31-3.27(m, 2H), 2.60(t, 2H), 2.20-2.11(m, 1H), 1.81-1.74(m, 3H), 1.57-1.55(m, 2H), 1.18(t, 3H, J=7.20Hz), 0.78(s, 9H), 0.01(s, 6H)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

170㎎ of the compound obtained in the above b) was dissolved in 10㎖ of tetrahydrofuran and then cooled to 0℃. To the resulting solution was added 1.65㎖ of 1.0M tetrabutylammonium fluoride solution, and the mixture was stirred for 45 minutes at the same temperature. After adding saturated saline, the reaction solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/ethyl acetate (1:1)] to obtain 120㎎ of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 8.66(brs, 1H), 7.35-7.29(m, 2H), 7.12-7.07(m, 1H), 7.00-6.93(m, 2H), 6.60-6.50(m, 2H), 6.13(s, 1H), 4.13(brs, 1H), 3.87(m, 2H), 3.39(s, 2H), 3.31(m, 2H), 2.57-2.54(m, 2H), 2.12-2.09(m, 1H), 1.77-1.74(m, 3H), 1.58-1.43(m, 2H), 1.09(t, 3H)

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

70㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 55㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(d, 1H), 7.54(d, 1H), 7.33(dd, 1H, J=8.35Hz, J=1.75Hz), 7.01(t, 1H), 6.60(m, 3H), 6.38(s, 1H), 4.18-4.14(m, 3H),

3.54-3.47(m, 4H), 2.73(t, 2H), 2.17-2.11(m, 1H), 1.92-1.73(m, 5H), 1.27(t, 3H)

Example 17 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(carbamoylmethoxy)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 18)

a) Synthesis of ethyl 2-[3-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidin-2-yl]-2-oxoethyl]phenoxy]acetate:

58㎎(0.146 mmole) of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)-acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 16-c) and 26㎕ of ethyl bromoacetate were dissolved in 5㎖ of dimethylformamide and then cooled to 0℃. After adding NaH, the reaction mixture was stirred for 30 minutes at the same temperature and then for one hour at room temperature. 5㎖ of water was added, and the reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over sodium sulfate and then filtered. The filtrate was concentrated, and the residue was purified with silica gel column chromatography [eluent: dichloromethane/ethyl acetate(1:1)] to obtain 53㎎ of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.42-7.37(m, 2H), 7.13-7.04(m, 2H), 6.76-6.70 (m, 2H), 6.63(m, 1H), 6.24(s, 1H), 4.43(s, 2H), 4.12-4.04(m, 3H), 3.96(m, 2H), 3.46(s, 2H), 3.33(m, 2H), 2.60(t, 2H), 2.21-2.14(m, 1H), 1.82-1.77(m, 3H), 1.58-1.54(m, 2H), 1.19-1.09(m, 6H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(carbamoylmethoxy)phenyl]-acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

38㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 18㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.81(d, 1H), 7.54(d, 1H), 7.32(m, 1H), 7.16(t,

1H), 6.83-6.78(m, 3H), 6.38(s, 1H), 4.37(s, 2H), 4.21-4.13(m, 3H), 3.60(d, 2H), 3.52-3.48(m, 2H), 2.74(t, 2H), 2.18-2.13(m, 1H), 1.97-1.86(m, 3H), 1.79-1.75(m, 2H), 1.26(t, 3H)

Example 18 : Synthesis of 2-[3-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]phenoxy]acetic acid (Compoud 19)

7㎎ of 1-ethyl-2-[2-(S)-1-[2-[3-(carbamoylmethoxy)phenyl]acetyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine obtained in Example 17 was dissolved in 0.5㎖ of acetic acid and 1㎖ of 3N HCl solution, and the resulting solution was heated to refluxing temperature and stirred for 3 hours under refluxing. The reaction solution was concentrated to remove the solvent and the residue was then purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 4㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.78(s, 1H), 7.50(d, 1H, J=7.58Hz), 7.35-7.28(m, 1H), 7.12-7.06(m, 1H), 6.75-6.69(m, 3H), 6.33(s, 1H), 4.24(s, 2H), 4.15-4.06(m, 3H), 3.58-3.47(m, 4H), 2.69-2.65(m, 2H), 2.14-2.09 (m, 1H), 1.94-1.88(m, 3H), 1.80-1.73(m, 2H), 1.22(t, 3H)

Example 19 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(trifluoro-methyl)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 20)

100㎎ of the compound I-a obtained in Example 1-l) and 120㎎ of 3-(trifluoromethyl)phenylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 80㎎ of the product, which was then treated according to the same procedure as Example 1-n) to obtain 34㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.94(m, 1H), 7.65-7.45(m, 6H), 6.46(s, 1H), 4.28(m, 3H), 3.82(m, 1H), 3.64(m, 2H), 2.87(t, 2H), 2.30(m, 1H), 2.05(m, 4H), 1.91-1.82(m, 2H), 1.36(m, 3H)

Example 20 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(2-nitrophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 21)

270㎎ of the compound I-a obtained in Example 1-l) and 250㎎ of 2-nitrophenylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 180㎎ of the white solid product. 60㎎ of the resulting product was then treated according to the same procedure as Example 1-n) to obtain 30㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.00(d, 1H), 7.76(m, 1H), 7.54-7.33(m, 5H), 6.31(s, 1H), 4.14(m, 3H), 3.96(m, 2H), 3.61(m, 2H), 2.72(t, 2H), 1.98-1.90(m, 6H), 1.80(m, 2H), 1.26(t, 3H)

Example 21 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[2-(methylsulfonylamino)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 22)

110㎎ of 1-ethyl-2-[2-[(S)-1-[2-(2-nitrophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was dissolved in 10㎖ of ethanol, and 15㎎ of 10% Pd/C was added thereto. The reaction mixture was stirred for 4 hours in hydrogen atmosphere at room temperature under normal pressure and then filtered under reduced pressure. The filtrate was distilled under reduced pressure and dried to obtain 110㎎ of the product. To 70 ㎎ of the resulting product thus obtained was added 3㎖ of pyridine and methanesulfonyl chloride was then slowly added thereto at 0℃. The reaction mixture was stirred for 3 hours at 0℃, and excess of ethyl acetate was added thereto. The organic layer was washed three times with water and 1N aqueous HCl solution, dried over sodium sulfate and then filtered under reduced pressure. The filtrate was distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:2)]. The fractions containing the desired product were combined and distilled under reduced pressure to obtain 80㎎ of the white foamy product. 74㎎ of the product thereby obtained was treated according to the same procedure as Example

1-n) to obtain 34㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(m, 1H), 7.53(d, 1H), 7.29(m, 2H), 7.16 (m, 2H), 7.03(t, 1H), 6.37(s, 1H), 4.19-4.12(m, 3H), 3.75(d, 1H), 3.59(m, 2H), 2.84(s, 3H), 2.74(t, 2H, J=8.09Hz), 1.96-1.91(m, 4H), 1.77(m, 2H), 1.25(t, 3H)

Example 22 : Synthesis of ethyl 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]benzoate (Compound 23)

a) Synthesis of 2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid:

985㎎ of the compound I-a obtained in Example 1-l) was dissolved in 40㎖ of ethanol, and 956㎎ of 75% homophthalic anhydride and 1.05㎖ of triethylamine were added thereto. The resulting solution was stirred for one hour at room temperature and distilled under reduced pressure to remove ethanol. To the residue was added water. The mixture was extracted with dichloromethane. The organic layer was then washed with 1N-HCl and water, dried over sodium sulfate, and then filtered. The filtrate was distilled under reduced pressure to obtain 1.57g of the title compound as a yellow foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.95(dd, 1H, J=7.80Hz, 1.30Hz), 7.50-7.44(m, 2H), 7.37-7.34(m, 2H), 7.17-7.25(m, 2H), 6.33(s, 1H), 4.28(s, 2H), 4.06-3.98(m, 3H), 3.94-3.91(m, 2H), 3.75-3.71(m, 2H), 2.24-2.21 (m, 1H), 2.10-2.05(m, 3H), 1.79-1.72(m, 2H), 1.25-1.21(m, 3H)

b) Synthesis of ethyl 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]benzoate:

150㎎ of the compound obtained in the above a) was treated according to the same proccedure as Example 1-n) to obtain 50㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.87(dd, 1H, J=7.85Hz, 1.40Hz), 7.76(s, 1H), 7.48(d, 1H, J=8.30Hz), 7.39(d, 1H, J=1.50Hz), 7.30-7.25(m, 2H), 7.18-7.15(m, 1H), 6.32(s, 1H), 4.14-4.09(m, 5H), 3.93(d, 2H, J=7.96Hz), 3.58-3.55(m, 2H), 2.74-2.71(m, 2H), 2.14-2.11(m, 1H), 1.96-1.93(m, 3H), 1.83-1.80(m, 2H), 1.19-1.11(m, 6H)

ES-MS : 475$(M+1)^+$

Example 23 : Synthesis of 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid (Compound 24)

150㎎ of 2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid obtained in Example 22-a) was treated according to the same procedure as Example 1-n) to obtain 28㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.68(s, 1H, J=7.60Hz), 7.62(dd, 1H, J=7.60 Hz, 2.00Hz), 7.43(d, 1H, J=8.30Hz), 7.22-7.15(m, 4H), 6.37(s, 1H), 4.15-4.10(m, 4H), 3.85(d, 1H, J=15.80Hz), 3.54-3.51(m, 2H), 2.77-2.74(m, 2H), 2.21-2.16(m, 1H), 1.98-1.93(m, 3H), 1.82-1.78 (m, 2H), 1.28-1.22(m, 3H)

ES-MS : 447$(M+1)^+$

Example 24 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 30)

a) Synthesis of 2-cyclopentyl-2-phenylacetyl chloride:

In a 100㎖ flask, 0.2g of 2-cyclopentyl-2-phenylacetic acid was introduced and 8㎖ of thionyl chloride was slowly added thereto at 0℃. The reaction mixture was stirred for 4 hours at 70℃ and then evaporated under reduced pressure to remove the solvent. The residue was dried under reduced pressure to obtain 0.2g of the title compound as a brown oil.

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrro-

lidin-2-yl]ethyl]indole-6-carbonitrile:

300㎎ of the compound I-a obtained in Example 1-l) and 30㎎ of 2-cyclo- pentyl-2-phenylacetyl chloride were treated according to the same procedure as Example 1-m) to obtain 30㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.53(m, 2H), 7.36-7.21(m, 6H), 6.28(s, 1H), 4.33(m, 1H), 4.13(m, 2H), 3.59(m, 1H), 3.38-3.30(m, 2H), 2.64(m, 3H), 2.07-1.92(m, 6H), 1.62(m, 6H), 1.26(m, 3H), 1.09(m, 2H)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

26㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 20㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.03(s, 1H), 7.40-7.18(m, 7H), 6.16(s, 1H), 4.27(m, 1H), 4.10 (m, 2H), 3.55(m, 1H), 3.37-3.28(m, 2H), 2.58(m, 3H), 2.01-1.90(m, 6H), 1.57(m, 6H), 1.25(m, 3H), 1.07(m, 2H)

Example 25 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-hydroxy-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 31)

250㎎ of the compound I-a obtained in Example 1-l) and 140㎎ of benzoylformic acid were dissolved in 10㎖ of dichloromethane, and 358㎎ of WSCIHCl was then slowly added thereto at 0℃. The reaction mixture was stirred at room temperature overnight, and excess of dichloromethane was added thereto. The organic layer was washed with water, dried over anhydrous magnesium sulfate and then filtered under reduced pressure. The filtrate was distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(2:1)]. The fractions containing the desired

product were combined and distilled under reduced pressure to obtain 83 mg of the product, which was then dissolved in 5mℓ of methanol, and 16mg of $NaBH_4$ was added at room temperature thereto. The mixture was stirred for one hour and then distilled under reduced pressure to remove the reaction solvent. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)]. The fractions containing the desired product were combined and then distilled under reduced pressure to obtain 15mg of the white solid product, which was then treated according to the same procedure as Example 1-n) to obtain 7 mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(m, 1H), 7.55(d, 1H), 7.34-7.23(m, 6H), 6.41(s, 1H), 4.23(m, 2H), 4.10(m, 1H), 3.49(m, 2H), 3.10(m, 1H), 2.78(t, 2H), 2.25(m, 1H), 1.91(m, 1H), 1.79-1.72(m, 5H), 1.30(t, 3H)

Example 26 : Synthesis of 1-methyl-2-[2-[(S)-1-[(R)-2-acetylamino-2-(4-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 32)

1.00g of the compound I-b obtained in Example 2-b) and 1.11g of (R)-2-(acetylamino)-2-(4-acetyloxyphenyl)acetic acid were treated according to the same procedure as Example 11-a) to obtain 1.67g of 4-[2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]-(R)-1-acetylamino-2-oxoethyl]phenyl acetate. 96mg of the compound thereby obtained was treated according to the same procedure as Example 1-n) to obtain 48mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.52(d, 1H, J=8.25Hz), 7.32(d, 1H, J=8.33Hz), 7.08(d, 2H, J=8.46Hz), 6.62(d, 2H, J=9.42Hz), 6.36 (s, 1H), 4.09(brs, 1H), 3.70(s, 3H), 1.86(s, 3H)

Example 27 : Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfonylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 37)

1.00g of (R)-(-)-2-phenylglycine, 10㎖ of 1,4-dioxane and 10㎖ of 2N aqueous NaOH solution were mixed, and 1.73g of $(BOC)_2O$ was slowly added at 0℃. The reaction mixture was stirred overnight at room temperature and distilled under reduced pressure to remove 1,4-dioxane. To the residue were added 50㎖ of water and 5㎖ of aqueous NH_4OH solution. The aqueous layer was washed with dichloromethane, acidified with c-HCl, and then extracted with ethyl acetate. The extract was dried over sodium sulfate and distilled under reduced pressure to obtain 1.6g of liquid (R)-2-[(tert-butoxy)carbonyl-amino]-2-phenylacetic acid. 507㎎ of (R)-2-[(tert-butoxy)carbonyl-amino]-2-phenylacetic acid and 450㎎ of 1-ethyl-2-[((S)-pyrrolidin-2-yl)ethyl]indole-6-carbonitrile were then treated according to the same procedure as Example 11-a) to obatin the product, which was then dissolved in dichloromethane. To the resulting solution, 4㎖ of trifluoroacetic acid was added. The reaction solution was stirred overnight at room temperature and extracted with excess of dichloromethane. The oragnic layer was neutralized with aqueous $NaHCO_3$ solution and then extracted with dichloromethane. The extract was dried over $MgSO_4$ and filtered under reduced pressure. The filtrate was then distilled under reduced pressure. The remaining residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)]. The fractions containing the desired product were combined and then distilled under reduced pressure to obtain 290㎎ of the white solid product. 80㎎ of the resulting product 1-ethyl-2-[2-[(S)-1-((R)-2-amino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was dissolved in 5㎖ of dichloromethane, and triethylamine (0.299 mmole) and methanesulfonyl chloride (0.299 mmole) were added at 0℃ thereto. The reaction mixture was stirred for 3 hours at 0℃ and excess of dichloromethane was added thereto. The organic layer was washed with water, dried over Na_2SO_4 and then filtered under reduced pressure. The filtrate was evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent : n-hexane/ethyl acetate(1:2)] to obtain 90㎎ of the white foamy solid product. Finally, 70㎎ of the resulting compound, 1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfo-

nylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was treated according to the same procedure as Example 1-n) to obtain 28㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.55(d, 1H, J=8.08Hz), 7.37-7.19(m, 6H), 6.39(s, 1H), 5.21(s, 1H), 4.23-4.12(m, 3H), 3.62(m, 1H), 3.12(m, 1H), 2.80(t, 2H), 2.68(s, 3H), 2.25(m, 1H), 1.93(m, 2H), 1.81-1.74(m, 6H), 1.30(t, 3H)

Example 28 : Synthesis of ethyl 2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]-aminolacetate (Compound 38)

192㎎ of 1-ethyl-2-[2-[(S)-1-((R)-2-amino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 27 and 120㎎ of ethyl bromoacetate were treated according to the same procedure as Example 1-m) to obtain 129㎎ of ethyl 2-[[(R)-2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetate. 120㎎ of the resulting compound was treated according to the same procedure as Example 1-n) to obtain 34㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.54(t, 1H), 7.48-7.22(m, 6H), 6.39(s, 1H), 4.52(s, 1H), 4.21(m, 2H), 4.06-4.01(m, 2H), 3.56(m, 2H), 3.05(m, 1H), 2.78(m, 2H), 2.25(m, 1H), 1.80-1.68(m, 7H), 1.29(t, 3H, J=7.10Hz), 1.13(m, 3H)

Example 29 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-2-(carbamoylmethylamino)-2-phenylacetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 39)

129㎎ of ethyl 2-[[(R)-2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate obtained in Example 28 was treated according to the same procedure as Example 1-n) to obtain 40㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.50(m, 1H), 7.34-7.13(m, 6H), 6.39(s, 1H), 4.46(s, 1H), 4.21(d, 2H), 4.08(m, 1H), 3.60(m, 1H), 3.24-2.97(m, 3H), 2.77(t, 2H, J=7.58Hz), 2.30(m, 1H), 1.92(m, 2H), 1.80-1.68(m, 5H), 1.28(t, 3H, J=6.93Hz)

Example 30 : Synthesis of 2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetic acid (Compound 40)

To 20㎎ of ethyl 2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate obtained in Example 28 was added concentrated HCl solution, and the reaction solution was stirred overnight while heating to 50-55℃ and then distilled under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: methanol] on NH-DM1020 silica to obtain 14㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.77(s, 1H), 7.46(t, 1H, J=7.58Hz), 7.36-7.21(m, 6H), 6.33(s, 1H), 4.51(s, 1H), 4.20-4.08(m, 4H), 3.02(m, 2H), 2.76(t, 3H, J=7.90Hz), 2.25(m, 1H), 1.91(m, 2H), 1.77-1.68(m, 5H), 1.26(m, 3H)

Example 31 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-cyclopentyl-acetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 42)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

100㎎ of the compound I-b obtained in Example 2-b) and 0.055㎖ of cyclopentylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 32㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.57(m, 2H), 7.29(m, 1H), 6.40(s, 1H), 4.25(d, 1H), 3.71(s, 3H), 3.48(m, 2H), 2.80(t, 2H), 2.28(m, 4H), 1.98(m,

4H), 1.88 (m, 2H), 1.75(m, 2H), 1.59(m, 3H), 1.16(m, 2H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

32㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 20㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.95(s, 1H), 7.27(m, 2H), 7.13-6.84(br, 2H), 6.12 (s, 1H), 4.03(m, 1H), 3.56(s, 3H), 3.33(m, 2H), 2.55(m, 2H), 2.13 (m, 4H), 1.84-1.70(m, 6H), 1.52-1.40(m, 5H), 1.03(m, 2H)
ES-MS : 380$(M+1)^+$

Example 32 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-acetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 43)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl] -ethyl]indole-6-carbonitrile:

100㎎ of the compound I-a obtained in Example 1-l) and 0.052㎖ of cyclopentylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 30㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.40(s, 1H), 4.28(m, 1H), 4.15(m, 2H), 3.50(m, 2H), 2.79(t, 2H), 2.30(m, 4H), 1.98(m, 3H), 1.87(m, 2H), 1.75(m, 2H), 1.59(m, 4H), 1.35(m, 3H), 1.18(m, 2H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl] -ethyl]indole-6-carboxamidine:

29㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 19㎎ of the

title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.06(m, 1H), 7.37(m, 2H), 6.91-6.52(br, 4H), 6.22(s, 1H), 4.17(m, 3H), 3.43(m, 2H), 2.67(m, 2H), 2.25(m, 4H), 1.94-1.71(m, 7H), 1.56(m, 4H), 1.21(m, 3H), 1.13(m, 2H)

ES-MS : 394$(M+1)^+$

Example 33 : Synthesis of ethyl 3-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate (Compound 44)

a) Synthesis of ethyl 3-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate:

In a 100㎖ flask, 1g of the compound I-a) obtained in Example 1-l) and 1g of α-ethylcarboxylate cyclopentane acetyl chloride were introduced and reacted according to the same procedure as Example 1-n) to obtain 0.5g of the title compound as a pale brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.28(m, 1H), 6.40(m, 1H), 4.31(m, 1H), 4.17(m, 4H), 3.70(m, 1H), 3.59(m, 1H), 3.30(d, 1H), 2.81(m, 2H), 2.68(m, 1H), 2.28(m, 1H), 2.02(m, 5H), 1.77(m, 2H), 1.61(m, 5H), 1.35(m, 3H), 1.22(m, 3H), 1.09(m, 1H)

b) Synthesis of ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate:

0.4g of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 0.31g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.98(m, 1H), 7.47(m, 1H), 7.33(m, 1H), 6.30(s, 1H), 4.16(m, 5H), 3.69-3.56(m, 2H), 3.30(d, 1H), 2.73(m, 3H), 2.25 (m, 1H), 1.98(m, 5H), 1.72-1.58(m, 7H), 1.31-1.21(m, 6H), 1.03(m, 1H)

ES-MS : 466(M+1)$^+$

Example 34 : Synthesis of 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoic acid (Compound 45)

In a 50mℓ flask, 80mg of ethyl 3-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate obtained in Example 33 was dissolved in 20mℓ of ethanol, and 10mℓ of 2N NaOH was added thereto. The reaction mixture was stirred for 10 hours at room temperature, neutralized with 10% aqueous citric acid solution, and then distilled under reduced pressure to remove the solvent. The residue was then purified with column chromatography [eluent: ethyl acetate/methanol (5:1)] on NH-DM1020 silica to obtain 51mg of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.87(s, 1H), 7.60(d, 1H), 7.38(d, 1H), 6.44(s, 1H), 4.28(m, 2H), 3.87(m, 1H), 3.65(m, 1H), 3.19(d, 1H), 2.89(m, 3H), 2.59(m, 1H), 2.24(m, 1H), 2.03(m, 5H), 1.84(m, 4H), 1.59(m, 4H), 1.32(m, 3H)

IR(KBr) : 3420, 2890, 1620 cm^{-1}

ES-MS : 439(M+1)$^+$, 462(M+Na)

Example 35 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 46)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile:

100mg of the compound I-a obtained in Example 1-l) and 88mg of cyclohexylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 60mg of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.30(m, 1H), 6.40(s, 1H), 4.28(m,

1H), 4.15(m, 2H), 3.47(t, 2H), 2.79(t, 2H), 2.28(m, 1H), 2.17(m, 1H), 1.99(m, 4H), 1.74-1.67(m, 7H), 1.38(m, 4H), 1.26(m, 3H), 0.94(m, 2H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine:

50㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 40㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.02(s, 1H), 7.73-7.54(br, 2H), 7.43(m, 2H), 6.25(s, 1H), 4.13(m, 3H), 3.48(m, 2H), 2.68(m, 2H), 2.21(m, 1H), 2.13(m, 1H), 1.92(m, 4H), 1.69-1.63(m, 7H), 1.27(m, 7H), 0.93(m, 2H)

ES-MS : 409(M+1)$^+$

Example 36 : Synthesis of 1-ethyl-2-[2-[(S)-[1-(3-phenylpropanoyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 50)

60㎎ of the compound I-a obtained in Example 1-l) and 40㎎ of 3-phenylpropanoic acid were reacted according to the same procedure as Example 11-a) to obtain 55㎎ of the product, which was then treated according to the same procedure as Example 1-n) to obtain 40㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 8.08(m, 1H), 7.61(m, 1H), 7.44(m, 1H), 7.34-7.17(m, 5H), 6.28(s, 1H), 4.19(m, 3H), 3.36-2.95(m, 2H), 2.92(t, 2H), 2.86(m, 4H), 2.69(m, 2H), 2.54(t, 2H), 2.27(m, 1H), 1.73-1.63 (m, 2H)

Example 37 : Synthesis of 1-methyl-2-[2-[(S)-1-((R)-2-acetylamino-3-phenylpropanoyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 53)

1.00g of the compound I-b obtained in Example 2-b) and 1.00g of (2)-2-acetylamino-3-phenylpropanoic acid were treated according to the same procedure as Example 11-a) to obtain 1.37g of N-[(R)-2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-benzylethyl]-ethanamide. 78㎎ of the compound thereby obtained was treated according to the same procedure as Example 1-n) to obtain 32㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.48(d, 1H), 7.18(d, 1H), 7.14(m, 5H), 6.31(s, 1H), 4.20-3.90(brs, 1H), 3.66(s, 3H), 2.84(s, 3H)

Example 38 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 57)

150㎎ of the compound I-b obtained in Example 2-b) was reacted with 96㎎ of chloroacetyl chloride under the same conditions as Example 1-m) to obtain the product, which was then dissolved in N,N-dimethylformamide. To the resulting solution were added 50㎎ of cyclopropylamine and K_2CO_3. The reaction mixture was stirred overnight at room temperature and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and then filtered. The filtrate was concentrated under reduced pressure to obtain the residue, which was then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane (4:1)] to obtain 120㎎ of the pale yellow solid product, 1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile. The product thereby obtained was treated according to the same procedure as Example 1-n) to obtain 45㎎ of the title compound as a pale yellow solid.

ES-MS : 382$(M+1)^+$

Example 39 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[cyclopropyl-(methylsulfonyl)aminolacetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 58)

100㎎ of 1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 38 was reacted with 60㎎ of methanesulfonyl chloride in 2㎖ of pyridine to obtain 90㎎ of the product, which was then treated according to the same procedure as Example 1-n) to obtain 55㎎ of the title compound as a pale yellow solid.

ES-MS : 460(M+1)$^+$

Example 40 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]-acetate (Compound 59)

300㎎ of the compound I-b obtained in Example 2-b) was reacted according to the same procedure as Example 38 to obtain 290㎎ of 1-methyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile, which was then reacted with 170㎎ of ethyl 2-bromo-acetate according to the same procedure as Example 1-m) to obtain 250㎎ of the yellow solid product. The resulting product was then treated according to the same procedure as Example 1-n) to obtain 85㎎ of the title compound as a pale yellow solid.

^{1}H-NMR(MeOH-d_4, ppm) : δ 7.80(d, 1H, J=3.28Hz), 7.56-7.51(m, 1H), 7.32(d, 1H, J=8.32Hz), 6.36(s, 1H), 4.08-3.93(m, 5H), 3.71(s, 3H), 3.37-3.34(m, 4H), 2.74-2.61(m, 3H), 2.18-2.11(m, 1H), 1.92(m, 1H), 1.80-1.77(m, 2H), 0.82-0.78(m, 3H), 0.58-0.65(m, 3H), 0.36 (m, 1H)

Example 41 : Synthsis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopentylamino]-acetate (Compound 60)

100㎎ of 1-methyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 40 and 60㎎ of cyclopentylamine were reacted according to the same procedure as

Example 38 to obtain 95㎎ of the yellow solid product, which was then reacted with ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 70㎎ of the pale yellow solid product. The resulting product was then treated according to the same procedure as Example 38 to obtain 48㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.54-7.51(m, 1H), 7.35-7.31(m, 1H), 6.37(s, 1H), 4.58(m, 2H), 4.38-4.31(m, 1H), 4.08-4.02(m, 2H), 3.91(m, 2H), 3.71(s, 3H), 3.65-3.61(m, 1H), 3.45-3.40(m, 2H), 2.79-2.73(m, 2H), 2.13-2.08(m, 1H), 1.93(m, 3H), 1.80-1.77(m, 4H), 1.57(br, 2H), 1.41(br, 4H), 0.82-0.78(m, 3H)

Example 42 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzylamino]acetate (Compound 61)

150㎎ of the compound I-b obtained in Example 2-b) was treated according to the same procedure as Example 1-m) to obtain the product, to which 70㎎ of ethyl 2-(benzylamino)acetate, 101㎎ of K_2CO_3 and 2.5㎖ of dimethylformamide were added. The resulting mixture was stirred overnight at room temperature and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(4:1)] to obtain 120㎎ of the pale yellow solid product, which was treated according to the same procedure as Example 1-n) to obtain 45㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.77-7.31(m, 4H), 7.28-7.19(m, 4H), 6.37(s, 1H), 4.89-4.45(m, 6H), 4.16-3.93(m, 3H), 3.69(d, 3H, J=8.84Hz), 3.44-3.37(m, 2H), 2.81-2.75(m, 2H), 2.18-1.71(m, 6H), 0.82-0.77 (m, 3H)

ES-MS : 504(M+1)$^+$

Example 43 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-

ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate (Compound 62)

a) Synthesis of 1-ethyl-2-[2-((S)-1-2-chloroacetylpyrrolidin-2-yl)ethyl]-indole-6-carbonitrile:

300㎎ of the compound I-a obtained in Example 1-l) and 130㎎ of chloroacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 351㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65-7.55(m, 2H), 7.40-7.30(m, 1H), 6.45(s, 1H), 4.40-4.30(m, 1H), 4.25-4.20(q, 2H), 4.10(s, 2H), 3.70-3.55(m, 2H), 2.90-2.80(t, 2H), 2.40-2.30(m, 1H), 2.20-1.95(m, 4H), 1.90-1.75 (m, 1H), 1.45-1.35(t, 3H)

b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate:

351㎎ of the compound obtained in the above a) was dissolved in dimethylformamide, and 306㎎ of K_2CO_3 and 238㎎ of N-ethylacetato-cyclopropylamine were added. The reaction mixture was stirred overnight at room temperature and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and filtered, and the filtrate was then concentrated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(4:1)] to obtain 373㎎ of the title compound as an oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65-7.55(m, 2H), 7.30-7.20(m, 1H), 6.50-6.40 (m, 1H), 4.35-4.10(m, 6H), 3.75-3.40(m, 6H), 2.90-2.80(m, 2H), 2.50-2.30(m, 1H), 2.20-1.95(m, 1H), 1.45-1.25(m, 1H), 0.95-0.70 (m, 2H), 0.55-0.50(m, 2H)

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl] -pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate:

55㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 24㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.70(m, 1H), 7.40(m, 1H), 7.20(m, 1H), 6.25(s, 1H), 4.55-4.40(d, 1H), 4.20-3.80(m, 5H), 3.50-3.10(m, 6H), 2.80-2.70(m, 2H), 2.20-1.65(m, 6H), 1.20-1.00(m, 6H), 0.75-0.65(m, 4H)

Example 44 : Synthesis of 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylaminolacetic acid (Compound 63)

40㎎ of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate obtained in Example 43 was dissolved in 50㎖ of ethanol, and 2㎖ of 2N NaOH was added thereto. The reaction mixture was stirred for 2 hours and then evaporated under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: ethanol] on NH-DM 1020 silica to obtain 25㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81-7.30(m, 3H), 6.37(s, 1H), 4.22-4.04(m, 3H), 3.56-3.43(m, 4H), 3.28(s, 2H), 2.81-2.67(m, 2H), 2.37(m, 1H), 2.23-1.70(m, 6H), 1.30-1.22(m, 3H), 0.64-0.25(m, 4H)

ES-MS : 440$(M+1)^+$

Example 45 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclo-propylaminolacetate (Compound 64)

a) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate:

500㎎ of 1-ethyl-2-[2-((S)-1-2-bromopropanoylpyrrolidin-2-yl)-ethyl]indole-6-carbonitrile and cyclopropylamine were dissolved in dry

N,N-dimethylformamide, and 104㎎ of $NaHCO_3$ and 20.4㎎ of KI were added thereto. The reaction mixture was heated under refluxing for one hour and, after water was added, extracted with ethyl acetate. The extract was dried and distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain the title compound in a quantitative yield.

b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate:

467㎎ of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate was dissolved in 15㎖ of acetonitrile, and diisopropylethylamine and ethyl-2-bromoacetate were added thereto. The reaction mixture was heated to 70°C and stirred for 4 hours. The reaction solution was concentrated under reduced pressure to obtain the residue, which was then purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 538㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.79(s, 1H), 7.58(d, 1H, J=8.10Hz), 7.28(d, 1H, J=7.96Hz), 6.45(s, 1H), 4.35-3.90(m, 8H), 3.60-3.40(m, 3H), 2.84 (m, 2H), 2.38-1.70(m, 8H), 1.42-1.13(m, 9H), 0.48(m, 3H),
ES-MS : 465$(M+1)^+$

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl] -pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate:

500㎎ of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 114㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.89(s, 1H), 7.61(d, 1H, J=8.29Hz), 7.42(d, 1H, J=8.22Hz), 6.44(s, 1H), 4.40-3.91(m, 6H), 3.70-3.40(m, 4H),

2.84(m, 2H), 2.40-1.70(m, 8H), 1.41(t, 3H), 1.23(m, 6H), 0.50(m, 3H)

ES-MS : 482(M+1)$^+$

Example 46 : Synthesis of 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]-acetic acid (Compound 65)

32㎎ of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate was treated according to the same procedure as Example 44 to obtain 27㎎ of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.82(s, 1H), 7.52(d, 1H), 7.32(d, 1H), 6.36(s, 1H), 4.30-3.80(m, 6H), 3.51-3.12(m, 3H), 2.73(m, 2H), 2.30-1.60 (m, 6H), 1.26(t, 3H), 1.13(m, 3H), 0.62-0.25(m, 4H)

ES-MS : 454(M+1)$^+$

Example 47 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]-acetate (Compound 66)

a) Synthesis of N-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl] (tert-butoxy)formamide:

406㎎ of the compound I-a obtained in Example 1-l) and 316㎎ of N-(tert-butoxy)carbonyl-D-alanine were reacted according to the same procedure as Example 11-a) to obtain 290㎎ of the title compound as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.42(s, 1H), 5.37 (d, 1H, J=8.44Hz), 4.47-4.39(m, 1H), 4.20-4.11(m, 3H), 3.74-3.40 (m, 2H), 2.79(t, 2H, J=7.91Hz), 2.39-1.77(m, 6H), 1.43(s, 9H), 1.37(t, 3H, J=7.23Hz), 1.25(d, 3H, J=7.13Hz)

b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]ethanoate:

274㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain the pale yellow solid product, which was then reacted with 0.076㎖ of ethyl 2-bromoacetate under the same conditions as Example 1-m) to obtain 187 ㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.62-7.55(m, 2H), 7.30(m, 1H), 6.43(s, 1H), 4.26 (brs, 1H), 4.21-4.13(m, 4H), 3.50, 3.64(m, 3H), 3.41(d, 1Ha, J=16.68Hz), 3.25(d, 1Hb, J=16.70Hz), 2.81(t, 2H, J=8.00Hz), 2.41-1.71(m, 6H), 1.37(t, 3II, J=7.21Hz), 1.27-1.23(m, 6H)

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]acetate:

183㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 144㎎ of the title compound as a pale yellow solid.

^{1}II NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.60-7.32(m, 2H), 6.40(s, 1H), 4.22-4.01(m, 5H), 3.86-3.72(m, 1H), 3.59-3.27(m, 4H), 2.84-2.68 (m, 2H), 2.26-1.77(m, 6H), 1.30(t, 3H, J=7.13Hz), 1.15-1.06(m, 6H)

IR(KBr) cm^{-1} : 3400, 2970, 1720, 1660, 1625, 1520, 1460

ES-MS : 442$(M+1)^+$

Example 48 : Synthesis of 2-[[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]acetic acid (Compound 67)

130㎎ of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]-(R)-1-methyl-2-oxoethyl]amino]acetate was treated according to the same procedure as Example 44 to obtain 60㎎ of the title

compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.76(s, 1H), 7.57-7.27(m, 2H), 6.35(s, 1H), 4.21-4.06(m, 3H), 3.66-3.40(m, 3H), 3.01(s, 2H), 2.82-2.73(m, 2H), 2.27-1.71(m, 6H), 1.27(t, 3H, J=7.08Hz), 1.13-1.05(m, 3H)
ES-MS : 414(M+1)$^+$

Example 49 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-hydroxymethyl-2-oxo-ethyl]aminolacetate (Compound 69)

a) Synthesis of N-[2-[[(S)-2-[2-(6-Cyano-1-ethylindol-2-yl)ethyl)pyrrolidinyl]-(R)-1-hydroxymethyl-2-oxoethyl]-(1,1-dimethylethyloxy)methanamide:

412㎎ of the compound I-a obtained in Example 1-l) and 348㎎ of N-(tert-butoxy)carbonyl-D-serine were reacted under the same conditions as Example 11-a) to obtain 110㎎ of the title compound as a viscous oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.41(s, 1H), 5.55 (brs, 1H), 4.49(m, 1H), 4.28-4.13(m, 3H), 3.90-3.52(m, 4H), 3.22(brs, 1H), 2.82-2.75(m, 2H), 2.40-1.77(m, 6H), 1.44(s, 9H), 1.38(t, 3H, J=8.76Hz)

b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-(1R)-1-hydroxymethyl-2-oxoethyl]amino]ethanoate:

109㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain the pale yellow solid product, which was then reacted with 0.029㎖ of ethyl 2-bromoacetate under the same conditions as Example 1-m) to obtain 20 ㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.62-7.55(m, 2H), 7.30(m, 1H), 6.41(s, 1H), 4.87-4.38(m, 2H), 4.31-4.11(m, 6H), 3.93-3.46(m, 4H), 2.77(m,

2H), 2.38-1.73(m, 6H), 1.40-1.25(m, 6H)

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-(1R)-1-hydroxymethyl-2-oxoethyl]amino]acetate:

20㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 10㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.70(s, 1H), 7.38(m, 2H), 6.27(s, 1H), 4.21-4.14(m, 5H), 3.57-3.47(m, 6H), 3.22-2.72(m, 4H), 2.29-1.70(m, 6H), 1.35(t, 3H, J=7.09Hz), 1.25(t, 3H, J=7.14Hz)

ES-MS : 458(M+1)$^+$

Example 50 : Synthsis of ethyl 4-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoate (Compound 72)

a) Synthesis of N-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]-N-cyclopropyl(1,1-dimethylethyloxy)methanamide:

375㎎ of 2-[2-((S)-1-2-chloroacetylpyrrolidin-2-yl)ethyl]-1- ethyl-indole-6-carbonitrile and 188㎎ of N-butyloxycarbonylcyclopropylamine were reacted under the same conditions as Example 45-b) to obtain 413㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.53(m, 2H), 7.30(m, 1H), 6.36(s, 1H), 4.31 (brs, 1H), 4.15(q, 2H, J=7.28Hz), 3.93(brs, 2H), 3.54-3.37(m, 2H), 2.81-2.76(m, 3H), 2.58-1.75(m, 6H), 1.47(s, 9H), 1.35(t, 3H, J=7.28Hz), 0.75-0.62(m, 4H)

b) Synthesis of ethyl 4-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-[N-cyclopropyl-(1,1-dimethylethyloxy)carbonylamino]-4-oxobutanoate:

413㎎ of the compound obtained in the above a) was dissolved in 8㎖ of tetrahydrofuran and cooled to -78℃. To this solution was slowly added dropwise 0.489㎖ of 2M LDA (lithium diisopropylamide) solution. The reaction mixture was then stirred for 40 minutes. 0.108㎖ of ethyl bromoacetate was added dropwise thereto, and the mixture was stirred for 2 hours at -30℃. After 0.5㎖ of water was added dropwise, the reaction solution was evaporated under reduced pressure, diluted with 150 ㎖ of dichloromethane, washed with 50㎖ of water, dried over sodium sulfate, and then filtered. The filtrate was evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:1)]. The fractions containing the pure desired product were combined and then evaporated under reduced pressure to obtain 167㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.59-7.54(m, 2H), 7.29(m, 1H), 6.37(s, 1H), 5.11 (brs, 1H), 4.19-4.09(m, 5H), 3.64-3.33(m, 2H), 3.22-3.12(m, 1H), 2.78(t, 2H, J=8.00Hz), 2.61-2.52(m, 1H), 2.36-1.70(m, 7H), 1.47(s, 9H), 1.35(t, 3H, J=7.19Hz), 1.23(t, 3H, J=7.10Hz), 0.75-0.61(m, 4H)

c) Synthesis of ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-3-(cyclopropylamino)-4-oxobutanoate:

165㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 33㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.77(s, 1H), 7.52-7.30(m, 2H), 6.33(s, 1H), 4.23-4.14(m, 3H), 4.01-3.84(m, 3H), 3.73-3.46(m, 2H), 2.85-2.48 (m, 4H), 2.12-1.71(m, 7H), 1.29(t, 3H, J=7.14Hz), 1.11-1.05(m, 3H), 0.40-0.22(m, 4H)

ES-MS : 468(M+1)$^+$

Example 51 : Synthesis of 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoic acid

(Compound 73)

26㎎ of ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoate was treated according to the same procedure as Example 44 to obtain 16㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.57(s, 1H), 7.31-7.06(m, 2H), 6.27(s, 1H), 4.22(brs, 1H), 4.13-4.05(m, 2H), 3.94-3.82(m, 2H), 3.74-3.66(m, 1H), 2.79-2.71(m, 2H), 2.46(m, 2H), 2.05-1.82(m, 7H), 1.22(t, 3H, J=7.13Hz), 0.36-0.31(m, 4H)

ES-MS : 440(M+1)$^+$

Example 52 : Synthesis of ethyl 2-[2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-N-cyclopentylacetylamino]-acetate (Compound 75)

100㎎ of the compound I-b obtained in Example 2-b) and 98㎎ of ethyl 2-(2-chloro-N-cyclopentylacetylamino)acetate were reacted under the same conditions as Example 42 to obtain the pale yellow solid product, which was then treated according to the same procedure as Example 1-n) to obtain 20㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81-7.32(m, 3H), 6.31(m, 1H), 4.52-4.43(m, 1H), 4.04-3.96(m, 2H), 3.80-3.48(m, 4H), 3.85(s, 3H), 3.11-2.66 (m, 4H), 2.55-1.03(m, 15H), 0.80(t, 3H, J=6.94Hz)

ES-MS : 482(M+1)$^+$

Example 53 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 77)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

In a 25㎖ flask, 30㎎ of 1-methyl-2-((S)-2-pyrrolidin-2-ylethyl)-

indole-6-carbonitrile and 36㎎ of 2-naphthalenesulfonyl chloride were dissolved in 3㎖ of dichloromethane, and 0.055㎖ of triethylamine was added at room temperature. The reaction mixture was stirred for 2 hours, diluted with water and then extracted three times with dichloromethane. The extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the pure desired product were combined and then evaporated to obtain 26.9㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.26(s, 1H), 7.88(m, 2H), 7.78(m, 1H), 7.73(d, 1H), 7.70(m, 2H), 7.64(m, 1H), 7.59(m, 1H), 7.34(d, 1H), 6.39(s, 1H), 3.79(m, 1H), 3.74(s, 3H), 3.50(m, 1H), 3.34(m, 1H), 2.93(m, 2H), 2.28(m, 1H), 1.99(m, 1H), 1.83(m, 1H), 1.65(m, 2H), 1.58(m, 1H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

27㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 14㎎ of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.11(s, 1H), 7.89-7.82(m, 3H), 7.64(d, 1H), 7.61-7.44(m, 4H), 7.43(d, 1H), 6.37(s, 1H), 3.77(s, 3H), 3.63(m, 1H), 3.37(m, 1H), 3.25(m, 1H), 2.85(m, 2H), 2.23(m, 1H), 1.91(m, 1H), 1.80(m, 1H), 1.59(m, 2H), 1.36(m, 1H),

ES-MS : 461(M+1)$^+$

Example 54 : Synthesis of 1-methyl-2-[2-((S)-1-naphthylsulfonyl-pyrrolidin-2-yl)ethyl]indole-6-carboxamidine (Compound 79)

a) Synthesis of 1-methyl-2-[2-((S)-1-naphthylsulfonylpyrrolidin-2-yl)-ethyl]indole-6-carbonitrile:

53㎎ of 1-naphthalenesulfonyl chloride was treated according to the same procedure as Example 53-a) to obtain 55㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.79(d, 1H), 8.12(d, 1H), 7.98(d, 1H), 7.99(d, 1H), 7.54(m, 4H), 7.40(m, 1H), 7.32(m, 1H), 6.25(s, 1H), 3.99(m, 1H), 3.57(s, 3H), 3.47-3.40(m, 2H), 2.74(m, 2H), 2.11(m, 1H), 1.87-1.81(m, 3H), 1.66(m, 2H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-naphthylsulfonylpyrrolidin-2- yl)-ethyl]indole-6-carboxamidine:

51㎎ of the compound obtained in the above a) was tretaed according to the same procedure as Example 1-n) to obtain 25㎎ of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.77(d, 1H), 8.06(m, 2H), 7.95(m, 2H), 7.67(d, 1H), 7.58(m, 1H), 7.52-7.40(m, 3H), 6.33(s, 1H), 3.94(m, 1H), 3.73(s, 3H), 3.50-3.42(m, 2H), 2.82(m, 2H), 2.14(m, 1H), 1.90(m, 2H), 1.74(m, 2H), 1.64(m, 1H)

Example 55 : Synthesis of 1-methyl-2-[2-((S)-1-acetylpyrrolidin-2-yl)ethyl]indole-6-carboxamidine (Compound 81)

490㎎ of 1-methyl-2-[2-((S)-1-acetylpyrrolidin-2-yl)ethyl]indole-6-carbonitrile was treated according to the same procedure as Example 1-n) to obtain 24㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.99(s, 1H), 7.33(m, 2H), 6.12(s, 1H), 4.01(bs, 1H), 3.54(s, 3H), 3.45-3.20(m, 2H), 2.54(bs, 2H), 2.20-1.40(m, 6H), 1.97(s, 3H)

Example 56 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylsulfonyl-acetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 82)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylsulfonylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

70㎎ of the compound I-b obtained in Example 2-b) and 81㎎ of phenylsulfonylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 12㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.94-7.91(m, 2H), 7.65(d, 1H, J=7.50Hz), 7.57-7.51(m, 4H), 7.29(d, 1H), 6.37(s, 1H), 4.23-4.10(m, 3H), 3.68(s, 3H), 3.75-3.66(m, 2H), 2.80(t, 3H, J=8.00Hz), 2.22-1.79(m, 6H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylsulfonylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

12㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 4㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.98-7.93(m, 3H), 7.74-7.62(m, 4H), 7.47(d, 1H, J=8.30Hz), 6.47(s, 1H), 4.15(bs, 1H), 3.82(s, 3H), 3.66-3.62(m, 2H), 3.33(s, 2H), 2.89(t, 2H), 2.20-1.84(m, 6H)

Example 57 : Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 83)

a) Synthesis of tert-butyl-(R)-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

17g of 1-ethyl-2-[((S)-pyrrolidin-2-yl)ethyl]indole-6-carbonitrile and 17.8g of (R)-N-(tert-butoxycarbonyl)proline were dissolved in dichloromethane, and 18.3g of WSCIHCl was added thereto. The reaction mixture was stirred for 2.5 hours at room temperature and, after water was added, extracted two times with dichloromethane. The extracts were combined, dried over $MgSO_4$ and then concentrated. The residue was purified with silica gel column chromatography [eluent:

dichloromethane/methanol(50:1)] to obtain 24g of the title compound as a white foam.

ES-MS : 465(M+1)$^+$

^{1}H NMR($CDCl_3$, ppm) : δ 7.60-7.51(m, 2H), 7.32-7.24(m, 1H), 6.41-6.33 (m, 1H), 4.52-4.47(m, 1H), 4.40-4.28(m, 1H), 4.16(q, J=7.20Hz, 2H), 3.79-3.62(m, 2H), 3.50-3.44(m, 2H), 2.83-2.79(m, 2H), 2.15-1.85(m, 10H), 1.43-1.40(m, 9H), 1.35(t, J=7.20Hz, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-[1-((R)-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile (Compound II-a):

24g of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 11g of the title compound as a white foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60-7.56(m, 2H), 7.31-7.26(m, 1H), 6.43(s, 1H), 4.41-4.37(m, 1H), 4.20-4.13(m, 3H), 3.64-3.61(m, 1H), 3.41-3.34(m, 3H), 2.81-2.78(m, 2H), 2.43-2.38(m, 2H), 2.17-1.82(m, 8H), 1.38(t, J=7.20Hz, 3H)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

50㎎ of the compound II-a obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 27㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.59-7.31(m, 2H), 6.39(s, 1H), 4.21-4.05(m, 3H), 3.68-3.46(m, 3H), 3.10-2.66(m, 4H), 2.27-1.52 (m, 10H), 1.30(t, 3H, J=7.15Hz)

IR(KBr) cm^{-1} : 3480, 1650, 1025

ES-MS : 382(M+1)$^+$

Example 58 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate

(Compound 84)

a) Synthesis of 1-methyl-2-[(2S)-[1-((2R)-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile (Compound II-b):

300㎎ of the compound I-b obtained in Example 2-b) was treated according to the same procedure as Examples 57-a) and 57-b) to obtain 200㎎ of the title compound as a white foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.63(s, 1H), 7.38(d, 1H), 7.10(d, 1H), 6.30(s, 1H), 4.25(t, 3H), 4.10-4.00(m, 1H), 3.65(s, 3H), 3.45-3.20(m, 2H), 2.80-2.70(m, 2H), 2.45-2.30(m, 1H), 2.30-2.15(m, 1H), 2.1-1.6(m, 1H)

b) Synthesis of methyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

50.0㎎ of the compound II-b obtained in the above a) was dissolved in dichloromethane and then cooled to 0℃. 24㎕ of triethylamine was added thereto, and after 20 minutes, 16㎕ of methyl bromoacetate was added dropwise. After 20 minutes, water was added and the reaction solution was extracted two times with dichloromethane. The extracts were combined, dried over $MgSO_4$ and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 28㎎ of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56-7.48(m, 2H), 7.32(m, 1H), 6.44(s, 1H), 4.28-4.15(bs, 1H), 3.86(m, 1H), 3.72(s, 3H), 3.67(s, 3H), 3.50(m, 2H), 2.82(m, 4H), 2.37-1.60(m, 12H)

c) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

26㎎ of the compound obtained in the above b) was dissolved in 15㎖ of ethanol solution saturated with HCl gas. The reaction solution

was allowed to stand at room temperature for one day and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vaccum pump. The dried product was then dissolved in 15㎖ of ethanol solution saturated with NH_3 gas. After one day, the reaction solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: ethyl acetate/ methanol(1:1)] on NH-DM1020 silica to obtain 12㎎ of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.94(s, 1H), 7.68(d, 1H), 7.47(d, 1H), 6.52(s, 1H), 4.30(bs, 1H), 3.92(m, 1H), 3.80-3.50(m, 7H), 3.28(m, 1H), 3.15-2.90(m, 3H), 2.40-1.75(m, 12H), 1.25(t, 3H)

Example 59 : Synthesis of ethyl 2-[(R)-2-[[2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]azetidinyl]carbonyl]pyrrolidinyl]acetate (Compound 85)

a) Synthesis of methyl (S)-2-azetidine carboxylate:

900㎎ of azetidine-(S)-2-carboxylic acid was treated according to the same procedure as Example 1-g) to obtain 1g of the title compound as a colorless oil.

b) Synthesis of methyl (S)-2-(tert-butoxycarbonyl)-2-azetidine carboxylate:

1g of the compound obtained in the above a) was treated according to the same procedure as Example 1-h) to obtain 1.8g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 4.61(m, 1H), 4.02(m, 1H), 3.89(m, 1H), 3.77(s, 3H), 2.50(m, 1H), 2.17(m, 1H), 1.42(s, 9H)

c) Synthesis of tert-butyl (S)-2-formylazetidine carboxylate:

1.7g of the compound obtained in the above b) was treated according to the same procedure as Example 1-i) to obtain 1.4g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 4.45(m, 1H), 3.92-3.77(m, 2H), 3.50(m, 1H), 2.30-2.08(m, 2H), 1.42(s, 9H)
ES-MS : 187$(M+2)^+$

d) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyllazetidine carboxylate:

3.8g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 1.3g of tert-butyl (S)-2-formylazetidine carboxylate obtained in the above c) were treated according to the same procedure as Example 1-j) to obtain 1.7g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60(m, 2H), 7.28(m, 1H), 6.70(s, 1H), 6.61(s, 1H), 6.55(d, 1H), 4.88(m, 1H), 4.21(q, 2H, J=7.2Hz), 3.92(m, 2H), 2.49(m, 1H), 2.10(m, 1H), 1.43(m, 9H), 1.38(m, 3H)

e) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-azetidine carboxylate:

1.6g of the compound obtained in the above d) was treated according to the same procedure as Example 1-k) to obtain 1.2g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.59(m, 2H), 7.28(m, 1H), 6.35(s, 1H), 4.36(m, 1H), 4.14(q, 2H, J=7.2Hz), 3.86(m, 2H), 2.83(m, 2H), 2.33(m, 2H), 2.10(m, 1H), 1.92(m, 1H), 1.46(s, 9H), 1.35(t, 3H, J=7.2Hz)

f) Synthesis of 2-[2-((S)-2-azetidinyl)ethyl]-1-ethylindole-6-carbonitrile:

1.1g of the compound obtained in the above e) was treated according to the same procedure as Example 1-l) to obtain 0.75g of the

title compound as a pale yellow solid.

g) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]azetidinyl]carbonyl]pyrrolidine carboxylate:

730㎎ of the compound obtained in the above f) was treated according to the same procedure as Example 11-a) to obtain 920㎎ of the title compound as a yellowish white oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.54(m, 2H), 7.28(m, 1H), 6.35(s, 1H), 4.54(m, 1H), 4.10(m, 3H), 3.53(m, 1H), 2.93(m, 1H), 2.48(m, 1H), 2.30(m, 2H), 2.07(m, 4H), 1.87(m, 2H), 1.44(s, 9H), 1.35(t, 3H, J=7.1Hz)

h) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)-2-azetidinyl]ethyl]indole-6-carbonitrile:

900㎎ of the compound obtained in the above g) was treated according to the same procedure as Example 1-l) to obtain 660㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.35(s, 1H), 4.53(m, 1H), 4.15(q, 2H, J=7.1Hz), 4.04(m, 1H), 3.63(m, 1H), 3.20(m, 1H), 2.88(m, 3H), 2.49(m, 2H), 2.02(m, 3H), 1.82(m, 2H), 1.70(m, 1H), 1.36(t, 3H, J=7.1Hz)

i) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]azetidinyl]carbonyl]pyrrolidinyl]acetate:

650㎎ of the compound obtained in the above h) and 0.31㎖ of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obtain 690㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.36(s, 1H), 4.55(m, 1H), 4.16(m, 5H), 3.51(m, 2H), 3.20(m, 1H), 2.92-2.75(m, 3H), 2.46(m, 2H), 2.09(m, 2H), 1.92(m, 4H), 1.36(t, 3H, J=7.1Hz), 1.25

(m, 3H)

j) Synthesis of ethyl 2-[(2)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]azetidinyl]carbonyl]pyrrolidinyl]acetate:

680㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-n) to obtain 90㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61(m, 1H), 7.53(m, 1H), 7.32(m, 1H), 6.33(s, 1H), 5.08-4.65(br, 2H), 4.54(m, 1H), 4.17(m, 5H), 3.69(m, 1H), 3.48(m, 2H), 3.41(m, 1H), 3.19(m, 1H), 2.88-2.73(m, 3H), 2.45(m, 2H), 2.13(m, 2H), 1.90(m, 4H), 1.36(t, 3H), 1.24(t, 3H)

IR(KBr) : 3250, 2900, 1720, 1620, 1460 cm^{-1}

ES-MS : 454(M+1)$^+$, 477(M+Na)

Example 60 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 86)

a) Synthesis of methyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

615㎎ of the compound II-a obtained in Example 57-b) was dissolved in dichloromethane, and 0.39㎖ of triethylamine was added thereto at room temperature. After 20 minutes, 280㎎ of methyl bromoacetate was added dropwise thereto. After 20 minutes, water was added and the reaction mixture was extracted three times with dichloromethane. The extracts were combined, dried over $MgSO_4$ and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 406㎎ of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60-7.47(m, 2H), 7.29(s, 1H), 6.44(s, 1H), 4.25 (bs, 1H), 4.20-4.10(m, 2H), 3.83(bs, 1H), 3.67(s, 3H), 3.60-3.43

(m, 2H), 3.25-3.17(m, 1H), 2.88-2.72(m, 3H), 2.38-1.62(m, 12H), 1.36(t, 3H)

b) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate :

406㎎ of the compound obtained in the above a) was dissolved in 30㎖ of ethanol solution saturated with HCl gas. The reaction solution was allowed to stand at room temperature for 2 days and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vaccum pump. The dried product was then dissolved in 30㎖ of ethanol solution saturated with NH_3 gas. After 2 days, the reaction solution was concentrated under reduced pressure and the residue thereby obtained was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 246㎎ of the title compound as a white foamy solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.88(s, 1H), 7.57(d, 1H), 7.40(d, 1H), 6.47(s, 1H), 4.43-4.18(m, 3H), 4.18-4.03(m, 2H), 3.78(m, 1H), 3.74-3.45 (m, 4H), 2.70(m, 2H), 2.12-1.60(m, 12H), 1.35(t, 3H), 1.18(t, 3H)

Example 61 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate (Compound 87)

a) Synthesis of tert-butyl (S)-2-(methoxycarbonyl)piperidine carboxylate:

In a 100㎖ flask, 5g of 1-((tert-butyl)oxycarbonyl)piperidine-(S)-2-carboxylic acid and 3.2g of $NaHCO_3$ were dissolved in 50㎖ of N,N-dimethylformamide, and 1.8㎖ of iodomethane was added thereto. The reaction solution was stirred for 8 hours at room temperature. After adding water, the reaction solution was extracted two times with ethyl acetate. The extracts were combined, dried over $MgSO_4$ and evaporated to obtain 4.5g of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 4.94-4.73(brs, 1H), 3.97(br, 1H), 3.73(s, 3H), 2.95-2.88(br, 1H), 2.21(m, 1H), 1.65(m, 3H), 1.45(br, 9H), 1.25(m, 2H)

b) Synthesis of tert-butyl (S)-2-formylpiperidine carboxylate:

3g of tert-butyl (S)-2-(methoxycarbonyl)piperidine carboxylate obtained in the above a) was treated according to the same procedure as Example 1-i) to obtain 2g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 9.59(s, 1H), 4.58(br, 1H), 4.08-3.89(br, 1H), 2.91(br, 1H), 2.14(m, 1H), 1.66(m, 3H), 1.46(br, 9H), 1.25(m, 2H)

c) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-piperidine carboxylate:

4g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 1.9g of tert-butyl (S)-2-formylpiperidinecarboxylate obtained in the above b) were treated according to the same procedure as Example 1-m) to obtain 1.8g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60(m, 2H), 7.29(m, 1H), 6.62(m, 1H), 6.43(m, 1H), 6.27(m, 1H), 5.39(m, 1H), 4.18(m, 2H), 4.11(m, 1H), 2.99(m, 1H), 1.79(m, 2H), 1.69(m, 2H), 1.48(m, 2H), 1.34(m, 3H), 1.25(m, 9H)

ES-MS : 380$(M+1)^+$

d) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-piperidine carboxylate:

1.5g of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 1.5g of the title compound as a brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.27(m, 1H), 6.35(s, 1H), 4.41(br,

1H), 4.15(m, 2H), 4.02(m, 1H), 2.68(m, 3H), 2.16(m, 1H), 1.83(m, 1H), 1.67-1.61(br, 6H), 1.45(s, 9H), 1.35(t, 3H, J=7.2Hz)

e) Synthesis of 1-ethyl-2-[2-(2-piperidyl)ethyl]indole-6-carbonitrile:

1.5g of the compound obtained in the above d) was treated according to the same procedure as Example 1-l) to obtain 1.1g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.47(m, 2H), 7.28(m, 1H), 6.31(s, 1H), 4.63-4.51(br, 1H), 4.11(q, 2H, J=7.2Hz), 3.18(m, 1H), 2.80(m, 3H), 1.95-1.85(m, 4H), 1.62(m, 1H), 1.40(m, 3H), 1.31(t, 3H, J=7.2Hz)
ES-MS : 282(M+1)$^+$

f) Synthesis of tert-butyl (R)-2-[[(2)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]piperidyl]carbonyl]pyrrolidine carboxylate:

1.1g of the compound obtained in the above e) was treated according to the same procedure as Example 11-a) to obtain 860㎎ of the title compound as a pale brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.54(m, 2H), 7.26(m, 1H), 6.33(s, 1H), 4.98(m, 1H), 4.64(m, 1H), 4.16(m, 2H), 3.78(m, 1H), 3.57(m, 1H), 3.47(m, 1H), 3.21(m, 1H), 2.74(m, 2H), 1.88(m, 3H), 1.73-1.64(br, 5H), 1.45(m, 9H), 1.38(m, 3H)
ES-MS : 479(M+1)$^+$

g) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)-2-piperidyl]ethyl]indole-6-carbonitrile:

670㎎ of the compound obtained in the above f) was treated according to the same procedure as Example 1-l) to obtain 440㎎ of the title compound as a pale yellow solid.

h) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-

ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate:

430㎎ of the compound obtained in the above g) and 0.19㎖ of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obatin 320㎎ of the title compound as a pale brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.53(m, 2H), 7.29(m, 1H), 6.36(s, 1H), 4.98(br, 1H), 4.12(m, 5H), 3.92(m, 2H), 3.59(m, 2H), 3.23(m, 1H), 3.06(m, 1H), 2.79-2.62(m, 4H), 2.16(m, 3H), 1.91-1.85(br, 5H), 1.28(m, 3H), 1.21(m, 3H)

ES-MS : 465(M+1)$^+$

i) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate :

300㎎ of the compound obtained in the above h) was treated according to the same procedure as Example 1-n) to obtain 60㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.88(s, 1H), 7.52(m, 1H), 7.30(m, 1H), 6.32(s, 1H), 4.97(br, 1H), 4.14(m, 4H), 3.93(m, 1H), 3.26(m, 1H), 3.11(m, 1H), 2.74(m, 2H), 2.18(br, 2H), 1.86(m, 4H), 1.67(br, 6H), 1.33(m, 3H), 1.23(m, 3H)

IR(KBr) : 3430, 2900, 1640 cm^{-1}

ES-MS : 482(M+1)$^+$

Example 62 : Synthesis of 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid (Compound 88)

720㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate was treated according to the same procedure as Example 44 to obtain 583㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.83(s, 1H), 7.55(d, 1H, J=8.34Hz), 7.25(d, 1H, J=8.36Hz), 6.36(s, 1H), 4.25-4.03(m, 3H), 3.62(m, 1H), 3.52-3.38(m, 2H), 3.16-3.03(m, 2H), 2.73(m, 2H), 2.37-1.46(m, 12H), 1.24(t, 3H)

ES-MS : 440(M+1)$^+$

IR(KBr) : 3200, 1600 cm^{-1}

Example 63 : Synthesis of 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidyl]carbonyl]pyrrolidinyl]acetic acid (Compound 89)

In a 50mℓ flask, 140mg of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate was dissolved in 10mℓ of ethanol, and 0.5mℓ of 2N NaOH was added thereto. The reaction solution was stirred for 3 hours at room temperature and evaporated under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: ethyl acetate/methanol (1:1)] on NH-DM1020 silica to obtain 60mg of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.87(m, 1H), 7.59(m, 1H), 7.42(m, 1H), 6.42 (m, 1H), 4.25(m, 2H), 3.64(m, 1H), 3.20(m, 1H), 3.15(m, 1H), 2.78(m, 2H), 2.31(m, 2H), 1.91(br, 2H), 1.77-1.68(br, 6H), 1.36(m, 3H)

IR(KBr) : 3400, 3000, 1650, 1600 cm^{-1}

ES-MS : 454(M+1)$^+$, 476(M+Na), 498(M+2Na)

Example 64 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 97)

a) Synthesis of (R)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

In a 1ℓ flask, 25g of (R)-4-hydroxy-L-proline was dissolved in

350㎖ of 4N-NaOH solution and then cooled to -20℃. To the resulting solution was added dropwise 41㎖ of benzyl chloroformate, and the reaction mixture was stirred for one hour at -20℃. After the reaction is completed, the reaction solution was adjusted to pH 4 with 2N aqueous HCl solution and then extracted two times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and evaporated to obtain 31.5g of the title compound as a white solid.

b) Synthesis of (S)-4-oxo-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

In a 500㎖ flask, 37.2g of CrO_3 and a small quantity of ice-water were mixed and 30.8㎖ of concentrated sulfuric acid was added dropwise thereto. The resulting solution was diluted with water to prepare 140㎖ of 8N-chromoic acid. In a 2ℓ flask, 31.5g of the compound obtained in the above a) was dissolved in 800㎖ of acetone, and 140㎖ of 8N-chromoic acid as prepared above was slowly added thereto. The reaction mixture was stirred for 2 hours at room temperature, and methanol was added dropwise to complete the reaction. The resulting precipitate was filtered and the filtrate was evaporated. The resiude was extracted two times with chloroform. The organic layers were combined, dried over $MgSO_4$ and then evaporated to obtain 28.4g of the title compound as a white solid.

^1H NMR($CDCl_3$, ppm) : δ 10.0(br, 1H), 7.30(s, 5H), 5.15(m. 2H), 4.90(m, 1H), 5.95(m, 2H), 2.95(m, 1H), 2.65(m, 1H)
ES-MS : 264$(M+1)^+$

c) Synthesis of phenylmethyl (S)-4,4-dimethoxy-2-(methoxycarbonyl)-pyrrolidine carboxylate:

In a 100㎖ flask, 4.0g of the compound obtained in the above b) was dissolved in 40㎖ of methanol, and 1.08㎖ of thionyl chloride was slowly added thereto at 0℃. The reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, the reaction

solution was evaporated under reduced pressure. The residue was extracted twice with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and evaporated to obtain 4.2g of the title compound as a colorless liquid.

^1H NMR($CDCl_3$, ppm) : δ 7.30(m, 5H), 5.30-5.0(m, 2H), 4.45(m, 1H), 3.80 (s, 2H), 3.55(m, 3H), 3.15(s, 6H), 2.35(m, 1H), 2.20(m, 1H)
ES-MS : 324$(M+1)^+$

d) Synthesis of methyl (S)-4-oxo-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylate:

In a 100mℓ flask, 3.0g of the compound obtained in the above c) was dissolved in 90mℓ of acetone and $TsOH \cdot H_2O$ was then added. The reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, the reaction solution was evaporated under reduced pressure, and the residue was extracted twice with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and evaporated to obtain 3.2g of the title compound as a colorless liquid.

^1H NMR($CDCl_3$, ppm) : δ 7.35(m, 5H), 5.20(m, 2H), 4.80(m, 1H), 4.0(s, 2H), 3.80(d, 3H), 2.95(m, 1H), 2.55(dd, 1H, J=18.85Hz, 2.67Hz)
ES-MS : 278$(M+1)^+$

e) Synthesis of methyl (S)-4-methylene-1-(benzyloxycarbonyl)pyrrolidine carboxylate:

In a 100mℓ flask, 10.0g of methyltriphenylphosphonium bromide was dissolved in 50mℓ of tetrahydrofuran, and tBuOK was slowly added thereto. The reaction mixture was stirred for 2 hours. 3.11g of the

compound obtained in the above d) which was dissolved in a small quantity of tetrahydrofuran was slowly added dropwise, and the mixture was stirred for 2 hours. After the reaction was quenched with a small quantity of water, the reaction solution was evaporated under reduced pressure, and the residue was extracted twice with ethyl ether. The organic layers were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:5)]. The fractions containing the desired product were combined and evaporated to obtain 1.5g of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.35(br, 5H), 5.20(m, 2H), 5.0(br, 2H), 4.55(m, 1H), 4.15(br, 2H), 3.65(d, 3H), 3.0(m, 1H), 2.65(d, 1H, J=16.0Hz)
ES-MS : 276(M+1)$^+$

f) Synthesis of methyl (S)-4-methyl-1-[tert-butoxycarbonyl]pyrrolidine-2-carboxylate:

1.5g of the compound obtained in the above e) was treated according to the same procedure as Example 1-k) to obtain 540㎎ of the yellow liquid product, which was then treated according to the same procedure as Example 1-h) to obtain 887㎎ of the title compound as a yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 4.20(m, 2H), 3.70(br, 3H), 3.0(t, 1H, J=10.05Hz), 2.40(m, 1H), 2.20(m, 1H), 1.50-1.30(br, 9H), 1.20(m, 1H), 1.0(br, 3H)
ES-MS : 244(M+1)$^+$

g) Synthesis of tert-butyl (S)-2-formyl-(S)-4-methylpyrrolidine carboxylate:

880mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-i) to obtain the title compound as a yellow liquid in a quantitative yield.

h) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-(S)-4-methylpyrrolidine carboxylate:

2.85g of 6-cyano-1-ethylindole-2-ethyl triphenylphosphonium bromide obtained in Example 1-f) and the compound obtained in the above g) were treated according to the same procedure as Example 1-j) to obtain 800㎎ of the title compound as a yellow fluorescent liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60(m, 2H), 7.25(m, 1H), 6.65(s, 1H), 6.60-6.40(br, 1H), 6.25(dd, 1H, J=15.63Hz, 6.89Hz), 4.40(m, 1H), 4.20 (q, 2H, J=7.24Hz), 4.0-3.45(m, 2H), 2.45-2.10(m, 2H), 1.60-1.30 (m, 12H), 1.25(m, 1H), 1.05(d, 3H, J=6.51Hz)

ES-MS : 380$(M+1)^+$

i) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-(S)-4-methylpyrrolidine carboxylate:

800㎎ of the compound obtained in the above h) was treated according to the same procedure as Example 1-k) to obtain 710㎎ of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.30(s, 1H), 4.15(q, 2H, J=7.24Hz), 3.90-3.60(m, 2H), 2.70(m, 3H), 2.30(m, 2H), 2.10(m, 1H), 1.85(m, 1H), 1.45(s, 9H), 1.35(t, 3H, J=7.24Hz), 1.25 (m, 1H), 1.10(d, 3H, J=6.46Hz)

ES-MS : 382$(M+1)^+$

j) Synthesis of 1-ethyl-2-[2-[(S)-((S)-4-methyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile:

430㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 401㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.45(m, 2H), 7.25(m, 1H), 6.25(s, 1H), 4.05(q,

2H, J=7.24Hz), 3.60(m, 2H), 3.35(m, 1H), 2.90-2.65(m, 3H), 2.40-2.20(m, 3H), 2.15(m, 1H), 1.25(t, 3H, J=7.24Hz), 1.10(d, 3H, J=6.46Hz)

ES-MS : 282(M+1)$^+$

k) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidine carboxylate:

400㎎ of the compound obtained in the above j) was treated according to the same procedure as Example 11-a) to obtain 370㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.30(m, 1H), 4.40(m, 1H), 4.10(m, 2H), 3.60(m, 2H), 3.40(m, 1H), 3.10(m, 1H), 2.80(m, 3H), 2.60-1.80(m, 6H), 1.80-1.10(m, 13H, J=6.46Hz), 1.05(d, 3H, J=6.46Hz)

ES-MS : 479(M+1)$^+$

l) Synthesis of 1-ethyl-2-[2-[(S)-4-methyl-1-((R)-pyrrolidin-2-ylcarbo-nyl)pyrrolidin-(S)-2-yl]ethyl]indole-6-carbonitrile:

270㎎ of the compound obtained in the above k) was treated according to the same procedure as Example 1-l) to obtain 220㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.40(s, 1H), 4.15(q, 2H, J=7.24Hz), 3.80(m, 1H), 3.25(m, 1H), 3.0(m, 2H), 2.80(m, 2H), 2.50(m, 1H), 2.20(m, 2H), 2.0-1.60(m, 4H), 1.50-1.20(m, 4H), 1.05 (d, 3H, J=6.46Hz)

ES-MS : 379(M+1)$^+$

m) Synthesis of 1-ethyl-2-[2-[(S)-4-methyl-1-((R)-pyrrolidin-2-ylcarbo-nyl)pyrrolidin-(S)-2-yl]ethyl]indole-6-carbonitrile:

150㎎ of the compound obtained in the above l) was treated

according to the same procedure as Example 1-m) to obtain 247㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.40(s, 1H), 4.20-4.00 (m, 4H), 3.95-3.75(m, 2H), 3.50(q, 2H), 3.20(m, 1H), 3.0-2.70(m, 4H), 2.60(m, 1H), 2.35(m, 1H), 2.20-1.70(m, 7H), 1.35(t, 3H, J=7.22Hz), 1.25(m, 4H), 1.10(d, 3H, J=6.43Hz)

ES-MS : 466$(M+1)^+$

n) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinyl]acetate :

240㎎ of the compound obtained in the above m) was treated according to the same procedure as Example 1-n) to obtain 71㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$) : δ 7.80(s, 1H), 7.50(d, 1H), 7.40(d, 1H), 6.40(s, 1H), 4.30-4.10(m, 4H), 3.90-3.70(m, 2H), 3.50(q, 2H), 3.20(m, 1H), 3.0-2.65(m, 4H), 2.60(m, 1H), 2.30(m, 1H), 2.20-1.70(m, 7H), 1.35(t, 3H, J=7.08Hz), 1.25(t, 3H, J=7.11Hz), 1.05(d, 3H, J=6.41Hz)

ES-MS : 482$(M+1)^+$

IR(KBr) : 3100, 2950, 1750, 1650 cm^{-1}

Example 65 : Synthesis of 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid (Compound 98)

42㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 64 was treated according to the same procedure as Example 44 to obtain 27㎎ of the title compound as a pale yellow solid.

^{1}H NMR(CD_3OD, ppm) : δ 7.70(s, 1H), 7.40(d, 1H), 7.20(d, 1H), 6.25(s, 1H), 4.20-3.80(m, 3H), 3.65(m, 1H), 3.15-2.50(m, 6H), 2.50-1.40

(m, 9H), 1.15(m, 3H), 0.95(m, 3H)

ES-MS : 454(M+1)$^+$

IR(KBr) : 3200, 2950, 2850, 1650 cm^{-1}

Example 66 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 99)

a) Synthesis of (4R)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic acid:

In a 250mℓ flask, 10g of (R)-4-hydroxypyrrolidine-(S)-2-carboxylic acid and 140mℓ of 4N NaOH were introduced and cooled to -20 ℃, and 17mℓ of benzyl chloroformate was slowly added. The reaction solution was stirred for one hour at -20℃ and extracted with ethyl ether and water. The ether layer was removed and the aqueous layer was acidified with 2N aqueous HCl solution and then extracted twice with ethyl acetate. The extracts were combined, dried over $MgSO_4$ and then evaporated to obtain 17.3g of the title compound as a colorless oil.

^1H NMR($CDCl_3$, ppm) : δ 7.30(m, 5H), 5.17(m, 2H), 4.52(m, 1H), 4.45(m, 1H), 3.60(m, 2H), 2.24(m, 2H)

b) Synthesis of 4-oxo-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic acid:

In a 1ℓ flask, 16g of the compound obtained in the above a) was dissolved in 600mℓ of acetone, and 64mℓ of 8N chromic acid was then slowly added at -10℃. The reaction mixture was stirred for 4 hours at -10℃, and 40mℓ of methanol was added thereto. The reaction solution was filtered. To the filtrate was added water, and the mixture was extracted twice with chloroform. The extracts were combined, dried over $MgSO_4$ and evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)] to obtain 12g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.34(s, 5H), 5.16(m, 1H), 5.09(m, 1H), 4.69(m, 1H), 3.92(s, 2H), 2.87(m, 1H), 2.64(m, 1H)
ES-MS : 264$(M+1)^+$

c) Synthesis of (S)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic acid:

In a 250㎖ flask, 4.6g of the compound obtained in the above b) was dissolved in 164㎖ of methanol, and 2.6g of $NaBH_4$ dissolved in 11㎖ of water was slowly added at -10℃. The reaction solution was stirred for about 2.5 hours at -10℃ to 0℃ and then evaporated to remove methanol. About 100㎖ of 2N aqueous NaOH solution was added to the residue and then stirred for 30 minutes at room temperature. The reaction solution was cooled to 0℃, acidified with hydrochloric acid and then extracted twice with ethyl acetate. The extracts were combined, dried over $MgSO_4$ and evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(3:1)] to obtain 3.2g of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.30(m, 5H), 6.90(br, 1H), 5.12(m, 2H), 4.43(m, 2H), 3.64(m, 1H), 3.54(m, 1H), 2.21(br, 2H)
ES-MS : 266$(M+1)^+$

d) Synthesis of (S)-4-methoxy-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic acid:

In a 100㎖ flask, 3g of the compound obtained in the above c) was dissolved in 40㎖ of tetrahydrofuran, and 0.95g of 60% NaH was slowly added. The reaction solution was stirred for one hour at room temperature, and 1.48㎖ of iodomethane was added. The reaction mixture was stirred for 3 hours at refluxing temperature and then for 10 hours at room temperature, and evaporated. To the residue was added water, and the mixture was acidified with 2N HCl and extracted twice with dichloromethane. The extracts were combined, dried over $MgSO_4$

and then evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(3:1)] to obtain 3.2g of the title compound as a pale brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.31(m, 5H), 5.17(m, 2H), 4.46(m, 1H), 3.94(m, 1H), 3.64(m, 2H), 3.26(s, 3H), 2.45-2.38(m, 1H), 2.22(m, 1H)
ES-MS : 280(M+1)$^+$, 302(M+Na)

e) Synthesis of phenylmethyl (S)-4-methoxy-(S)-2-(methoxycarbonyl)-pyrrolidine carboxylate:

In a 100mℓ flask, 13mℓ of methanol was introduced and 0.93mℓ of thionyl chloride was slowly added thereto at 0℃. 3.1g of the compound obtained in the above d) which was dissolved in 11mℓ of methanol was added thereto, and the reaction mixture was stirred for 2 hours at refluxing temperature and then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate (3:1)] to obtain 2.4g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.31(m, 5H), 5.17(m, 2H), 4.45(m, 1H), 3.93(m, 1H), 3.72(m, 2H), 3.67(s, 3H), 3.25(s, 3H), 2.32-2.22(m, 2H)
ES-MS : 294(M+1)$^+$

f) Synthesis of phenylmethyl (S)-2-formyl-(S)-4-methoxypyrrolidine carboxylate:

2.3g of the compound obtained in the above e) was treated according to the same procedure as Example 1-i) to obtain 1.4g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.33(m, 5H), 5.16(m, 2H), 4.19(m, 1H), 3.92(m, 1H), 3.73(m, 1H), 3.52(m, 1H), 3.22(s, 3H), 2.38(m, 1H), 2.14(m, 1H)
ES-MS : 264(M+1)$^+$

g) Synthesis of phenylmethyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-(S)-4-methoxypyrrolidine carboxylate:

2.3g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 1.2g of phenylmethyl 2-formyl-4-methoxypyrrolidine carboxylate were reacted according to the same procedure as Example 1-j) to obtain 1.7g of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58(br, 2H), 7.36-7.21(br, 6H), 6.64(m, 1H), 6.47(m, 1H), 5.14(m, 2H), 4.21(m, 1H), 4.00(m, 2H), 3.68-3.58(br, 2H), 3.34(s, 3H), 2.34(m, 1H), 1.23-1.20(m, 4H)
ES-MS : 452(M+Na)

h) Synthesis of 1-ethyl-2-[2-[(S)-((S)-4-methoxy)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile:

1.6g of the compound obtained in the above g) was treated according to the same procedure as Example 1-k) to obtain 500㎎ of the title compound as a brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58(m, 2H), 7.27(m, 1H), 6.30(s, 1H), 4.16(q, 2H, J=7.1Hz), 3.91(m, 1H), 3.28(s, 3H), 3.15(m, 2H), 2.92-2.78(m, 4H), 2.24(m, 1H), 2.02(m, 2H), 1.34(t, 3H, J=7.1Hz)
ES-MS : 298(M+1)$^+$

i) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidine carboxylate:

450㎎ of the compound obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 590㎎ of the title compound as a pale brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.28(m, 1H), 6.39(m, 1H), 4.37(m, 1H), 4.16(m, 2H), 4.03(m, 1H), 3.62(m, 1H), 3.32(s, 3H), 2.82(m, 2H), 2.12-1.96(br, 4H), 1.85(m, 2H), 1.40(m, 9H), 1.33(m, 3H)

j) Synthesis of 1-ethyl-2-[2-[(S)-4-methoxy-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-(S)-2-yl]ethyl]indole-6-carbonitrile:

580㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 450㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.32(m, 1H), 6.42(s, 1H), 4.28(m, 1H), 4.15(m, 2H), 4.01(m, 1H), 3.75(m, 1H), 3.65(m, 1H), 3.33(s, 3H), 3.21(m, 1H), 2.80(m, 2H), 2.45(m, 1H), 2.10(m, 2H), 1.99-1.79(br, 7H), 1.36(m, 3H)

k) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

440㎎ of the compound obtained in the above j) and 0.19㎖ of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obtain 380㎎ of the title compound as a pale yellow oil.

ES-MS : 481$(M+1)^+$

l) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

360㎎ of the compound obtained in the above k) was treated according to the same procedure as Example 1-n) to obtain 90㎎ of the title compound as a pale yellow solid.

IR(KBr) : 3300, 3000, 1750, 1640 cm^{-1}

ES-MS : 498$(M+1)^+$

Example 67 : Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]propionate (Compound 109)

a) Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]propionate:

300㎎(0.823 mmole) of 1-ethyl-2-[2-[(S)-1-[((R)-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was dissolved in 15 ㎖ of acetonitrile, and 0.29㎖(1.646 mmole) of diisopropylethylamine and 0.22㎖(1.646 mmole) of ethyl 2-bromopropionate were added thereto. The reaction mixture was heated to 70℃, stirred for 4 hours, and then concentrated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 310㎎ of the title compound as a pale yellow oil.

ES-MS : 464 $(M+1)^+$

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.56(m, 2H), 7.34-7.28(m, 1H), 6.46(s, 1H), 4.31(br, 1H), 4.21-4.14(m, 4H), 3.80-3.75(m, 1H), 3.61-3.53(m, 3H), 3.23-3.19(m, 1H), 2.86-2.81(m, 3H), 2.34-2.31(m, 1H), 2.01-1.77(m, 9H), 1.42-1.36(m, 3H), 1.32-1.22(m, 6H)

b) Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]propionate:

310㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 220㎎ of the title compound as a pale yellow foam.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.93-7.89(m, 1H), 7.64-7.58(m, 1H), 7.48-7.42(m, 1H), 6.46-6.42(m, 1H), 4.34-4.30(m, 3H), 4.18-4.14(m, 2H), 3.91-3.81(m, 1H), 3.65-3.61(m, 3H), 3.15-3.11(m, 1H), 2.88-2.81(m, 3H), 2.21-1.85(m, 10H), 1.42-1.27(m, 9H)

IR(KBr) : 3300, 2980, 1720. 1680, 1640, 1540 cm^{-1}

ES-MS : 482$(M+1)^+$

Example 68 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate (Compound 110)

a) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate:

100㎎ of the compound II-a obtained in Example 57-b) and 80㎕ of ethyl 2-bromoacetate were reacted according to the same procedure as Example 45-b) to obtain 88㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58(m, 2H), 7.27(m, 1H), 6.40(d, 1H), 4.38(m, 1H), 4.15(m, 4H), 3.69(m, 1H), 3.54(m, 2H), 3.30-3.10(m, 1H), 2.82(m, 3H), 2.30(m, 1H), 2.18-1.55(m, 12H), 1.42-1.17(m, 6H), 0.89(m, 3H)

b) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate:

88㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 24㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.00-6.24(m, 4H), 4.24(m, 5H), 3.64(m, 1H), 3.52(m, 2H), 3.41-3.10(m, 3H), 2.83(m, 5H), 2.31(m, 1H), 2.18-1.54(m, 8H), 1.44-1.10(m, 6H), 0.84(m, 3H)

Example 69 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate (Compound 111)

a) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

135㎎ of the compound II-a obtained in Example 57-b) and 155㎕ of ethyl 2-bromoacetate were reacted according to the same procedure as Example 45-b) to obtain 112㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58(m, 2H), 7.28(d, 1H), 6.45(d, 1H, J=

8.20Hz), 4.30-4.00(m, 6H), 3.71-3.31(m, 3H), 3.25-3.05(m, 1H), 2.82(m, 3H), 2.45-2.20(m, 1H), 2.13-1.55(m, 11H), 1.38-1.12(m, 10H), 0.85(t, 2H), 0.75(t, 1H)

b) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

112㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 73㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.82(s, 1H), 7.62(d, 1H, J=11.71Hz), 7.34(d, 1H, J=7.80Hz), 6.46(d, 1H, J=11.14Hz), 4.40-4.05(m, 6H), 3.75-3.40(m, 3H), 3.30-3.05(m, 1H), 2.99-2.66(m, 3H), 2.50-2.30(m, 1H), 2.13-1.52(m, 11H), 1.50-1.10(m, 10H), 0.90-0.70(m, 3H)
ES-MS : 524(M+1)$^+$

Example 70 : Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-phenylacetate (Compound 112)

a) Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-phenylacetate:

300㎎ of the compound II-a obtained in Example 57-b) ad 300㎎ of ethyl 2-bromophenyl acetate were reacted according to the same procedure as Example 45-b) to obtain 300㎎ of the title compound as a pale yellow foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.63-7.57(m, 2H), 7.51-7.48(m, 2H), 7.34-7.29 (m, 4H), 6.43(s, 1H), 4.65(s, 1H), 4.24-4.19(m, 3H), 4.11-4.04(m, 3H), 3.45-3.41(m, 2H), 3.06-3.03(m, 1H), 2.84-2.71(m, 3H), 2.30-2.20(m, 2H), 1.98-1.82(m, 8H), 1.42(t, J=7.20Hz, 3H), 1.08(t, J=7.10Hz, 3H)
ES-MS : 526(M+1)$^+$

b) Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-phenylacetate:

130㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 80㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.04-7.95(m, 1H), 7.78-7.67(m, 1H), 7.50-7.45(m, 2H), 7.31-7.24(m, 4H), 6.51(m, 1H), 4.52(m, 1H), 4.37-4.34(m, 2H), 4.09-4.04(m, 3H), 3.49-3.44(m, 1H), 3.20-3.09(m, 2H), 2.98-2.65(m, 4H), 2.20-1.75(m, 10H), 1.47-1.42(m, 3H), 1.13-1.06(m, 3H)

ES-MS : 544$(M+1)^+$

Example 71 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]-pyrrolidinyl]-2-(3-bromo-4-methoxyphenyl)acetate (Compound 113)

a) Synthesis of ethyl-2-bromo-2-(3-bromo-4-methoxyphenyl)acetate:

4.3g(0.0259 mole) of 4-methoxyphenylacetic acid was dissolved in 10㎖ of thionyl chloride, and the resulting solution was stirred for 18 hours at 70℃ and then cooled to room temperature. To the reaction solution was added 50㎖ of carbon tetrachloride and then added 5.54g (0.0331 mole) of N-bromosuccinimide and 5 drops of 48% aqueous HBr solution. The resulting mixture was stirred for 4 hours at refluxing temperature and filtered to remove the unsoluble materials. 50㎖ of ethanol was added to the filtrate and the mixture was stirred for 30 minutes and then evaporated under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:9)] to obtain 1.5g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.72(d, J=2.23Hz, 1H), 7.45(dd, 1H, J=2.22Hz, 8.50Hz), 6.93(d, 1H, J=8.50Hz), 5.28(s,1H), 4.32-4.25(m,2H), 3.93

(s, 3H), 1.32(t, 3H, J=7.00Hz)

b) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-(3-bromo-4-methoxyphenyl)-acetate:

100㎎ of the compound II-a obtained in Example 57-b) and 80㎎ of the compound obtained in the above a) were reacted according to the same procedure as Example 1-m) to obtain 170㎎ of the title compound as a pale yellow foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.69-7.57(m, 3H), 7.40-7.29(m, 2H), 6.82(m, 1H), 6.44(m, 1H), 4.60(m, 1H), 4.24-4.21(m, 3H), 4.09-3.98(m, 3H), 3.78(m, 3H), 3.41-3.37(m, 2H), 3.24-3.05(m, 2H), 2.81-2.75 (m, 2H), 2.21-1.72(m, 10H), 1.45-1.39(m, 3H), 1.24-1.08(m, 3H)

c) Synthesis of ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-(3-bromo-4-methoxyphenyl)-acetate:

170㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 70㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.85-7.75(m, 1H), 7.57-7.42(m, 2H), 7.33-7.29(m, 2H), 6.96-6.78(m, 1H), 6.36-6.33(m, 1H), 4.52(s, 1H), 4.21-4.18(m, 3H), 4.04-3.86(m, 3H), 3.73(m, 3H), 3.22-3.02(m, 2H), 2.91-2.78(m, 2H), 2.65-2.60(m, 2H), 2.10-1.65(m, 10H), 1.33-1.25(m, 3H), 1.09-1.00(m, 3H)

ES-MS : 653$(M+1)^+$

IR(KBr) : 3380, 3020, 1740, 1635, 1540 cm^{-1}

Example 72 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 114)

681mg of methyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate was dissolved in 25mℓ of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for one day at room temperature and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vaccum pump. The dried product was dissolved in 25mℓ of ethanol solution saturated with NH_3 gas, and the resulting solution was allowed to stand for 3 days at room temperature and then concentrated. The residue was purified with column chromatography [eluent: ethyl acetate/ethanol(1:1)] on NH-DM1020 silica to obtain 553mg of the title compound as a colorless solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.53(d, 1H, J=8.42Hz), 7.32(d, 1H, J=8.27Hz), 6.40(s, 1H), 4.18(m, 3H), 3.57(m, 1H), 3.46(m, 4H), 2.84(m, 2H), 2.51-1.7(m, 12H), 1.28(t, 3H)
ES-MS : 439(M+1)$^+$

Example 73 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(N-cyclopropylcarbamoyl)methyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine (Compound 115)

250mg of the compound II-a obtained in Example 57-b) and 92mg of N-cyclopropyl-2-chloroethanamide were reacted under the same conditions as Example 42 to obtain 125mg of the pale yellow solid product, which was then treated according to the same procedure as Example 1-n) to obtain 93mg of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.13(d, 1H, J=3.75Hz), 7.88(s, 1H), 7.61-7.38(m, 2H), 6.40(s, 1H), 4.27-4.13(m, 3H), 3.56-3.08(m, 3H), 2.90(s, 2H), 2.82(t, 2H, J=6.91Hz), 2.72-2.65(m, 1H), 2.50-1.67(m, 12H), 1.35 (t, 3H, J=7.20Hz), 0.88-0.50(m, 4H)
ES-MS : 479(M+1)$^+$

Example 74 : Synthesis of ethyl (S)-2-[2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-

acetylamino]propanoate (Compound 116)

250㎎ of the compound II-a obtained in Example 57-b) and 133㎎ of ethyl-(S)-2-(2-chloroacetylamino)propa- noate were reacted under the same conditions as Example 42 to obtain 260㎎ of the pale yellow solid product, which was then treated according to the same procedure as Example 1-n) to obtain 96㎎ of the title compound as a pale yellow solid.

ES-MS : 539(M+1)$^+$

Example 75 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine (Compound 117)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

700㎎ of the compound II-a obtained in Example 57-b) and 500㎎ of α-bromo-γ-butyrolactone were reacted according to the same procedure as Example 45-b) to obtain 650㎎ of the title compound as a white foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58-7.53(m, 2H), 7.30-7.26(m, 1H), 6.46(s, 1H), 4.39-4.34(m, 1H), 4.26(br, 1H), 4.21-4.13(m, 3H), 3.86-3.63(m, 3H), 3.51-3.45(m, 1H), 3.30-3.22(m, 1H), 2.96-2.90(m, 1H), 2.83-2.79(m, 2H), 2.39-2.11(m, 4H), 2.03-1.96(m, 4H), 1.84-1.66(m, 4H), 1.35(t, J=7.30Hz, 3H)

ES-MS : 449(M+1)$^+$

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

450㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 370㎎ of the

title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.85-7.79(m, 2H), 7.56-7.52(m, 1H), 6.41(m, 1H), 4.23-4.18(m, 2H), 4.13-4.10(m, 1H), 3.64-3.59(m, 1H), 3.50-3.31(m, 4H), 3.07-2.87(m, 1H), 2.81-2.76(m, 2H), 2.68-2.61(m, 1H), 2.24-2.08(m, 2H), 1.92-1.71(m, 10H), 1.30(t, J=7.05Hz, 3H)
ES-MS : 483(M+1)$^+$
IR(KBr) : 3340, 3220, 2980, 1680, 1630, 1540 cm^{-1}

Example 76 : Synthesis of 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-hydroxy-butanoic acid (Compound 118)

250㎎ of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(1-carbamoyl-3-hydroxy-propyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine was treated according to the same procedure as Example 44 to obtain 180㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80-7.74(m, 1H), 7.56-7.48(m, 1H), 7.32-7.26(m, 1H), 6.39-6.34(m, 1H), 4.31-4.03(m, 4H), 3.69-3.64(m, 1H), 3.56-3.29(m, 4H), 3.04-2.96(m, 1H), 2.78(br, 3H), 2.20(br, 1H), 2.01-1.56(m, 11H), 1.29-1.24(m, 3H)
ES-MS : 484(M+1)$^+$
IR(KBr) : 3400, 3000, 1630, 1580 cm^{-1}

Example 77 : Synthesis of 1-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid (Compound 123)

a) Synthesis of diethyl-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butane-1,4-dioate:

230㎎(0.525 mmole) of ethyl-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate was dissol- ved in 15㎖ of tetrahydrofuran and then cooled to -78℃. 0.79㎖ of lithium

bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran) was added dropwise thereto, and the reaction mixture was stirred for 30 minutes. 0.09㎖(0.787 mmole) of ethyl bromoacetate diluted with 5㎖ of tetrahydrofuran was added dropwise thereto, and the resulting mixture was stirred for one hour. After water was added, the reaction solution thereby obtained was extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(40:1)] to obtain 180㎎ (Yield : 63.9%) of the title compound as a pale yellow foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.51(m, 2H), 7.27(dd, 1H, J=1.30Hz, 8.10Hz), 6.46(s, 1H), 4.33(br, 1H), 4.21-4.06(m, 6H), 3.95-3.91(m, 1H), 3.84-3.80(m, 1H), 3.67-3.63(m, 1H), 3.49-3.45(m, 1H), 3.17-3.11(m, 1H), 2.99-2.91(m, 1H), 2.82-2.74(m, 3H), 2.60-2.55 (m, 1H), 2.38-2.31(m, 1H), 2.02-1.95(m, 5H), 1.81-1.74(m, 4H), 1.38-1.17(m, 9H)

ES-MS : 537$(M+1)^+$

b) Synthesis of 1-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid:

400㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 180㎎ of diethyl 2-[(2)-2-[[(2)-2-[2-(6-amidino-1-ethylindole-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butane-1,4-dioate, which was then treated according to the same procedure as Example 44 to obtain 120㎎ of the title compound as white solid.

^{1}H NMR(MeOH-d_4) : δ 7.79(s, 1H), 7.51-7.47(m, 1H), 7.32-7.29(m, 1H), 6.42(s, 1H), 4.57(br, 1H), 4.23-4.19(m, 2H), 3.70(br, 2H), 3.52-3.48(m, 2H), 2.86-2.74(m, 4H), 2.60-2.54(m, 2H), 2.36-2.31(m, 1H), 2.12-2.09(m, 2H), 2.02-1.92(m, 6H), 1.66-1.61(m, 1H), 1.33-1.28(m, 3H)

ES-MS : 498$(M+1)^+$

IR(KBr) : 3400, 3000, 1630, 1580 cm^{-1}

Example 78 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 125)

130㎎(0.269 mmole) of 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-hydroxybutanoic acid was dissolved in 5㎖ of 3N-HCl, and the resulting solution was stirred for 18 hours at room temperature and then evaporated under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(3:1) on NH-DM1020 silica to obtain 70㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.54-7.51(m, 1H), 7.34-7.30(m, 1H), 6.39(s, 1H), 4.31-4.20(m, 3H), 4.11-4.07(m, 2H), 3.68-3.64 (m, 1H), 3.58-3.46(m, 4H), 2.80-2.75(m, 2H), 2.67-2.61(m, 1H), 2.30-2.12(m, 3H), 1.93-1.87(m, 4H), 1.80-1.73(m, 5H), 1.31-1.27 (m, 3H)

ES-MS : 466$(M+1)^+$

IR(KBr) : 3400, 3020, 1770, 1640, 1540 cm^{-1}

Example 79 : Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate (Compound 126)

a) Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate:

400㎎ of the compound II-a obtained in Example 57-b) and 0.173 ㎖ of ethyl 4-bromobutanoate were reacted according to the same procedure as Example 45-b) to obtain 453㎎ of the title compound as a viscous oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.59-7.53(m, 2H), 7.29(m, 1H), 6.47(s, 1H),

4.32-4.11(m, 3H), 4.05-3.99(m, 2H), 3.61(m, 2H), 3.27-3.18(m, 2H), 2.77(m, 2H), 2.66-1.62(m, 16H), 1.36(t, 3H, J=7.18Hz), 1.17 (t, 3H, J=7.14Hz)

b) Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate :

453㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 228㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.56-7.31(m, 2H), 6.40(s, 1H), 4.21(m, 2H), 4.10(brs, 1H), 3.91-3.80(m, 2H), 3.63-3.47(m, 2H), 3.08(m, 1H), 2.77(m, 2H), 2.52-1.65(m, 18H), 1.30(t, 3H, J=7.17 Hz), 1.08-0.97(m, 3H)
IR(KBr) : 3300, 3000, 1740, 1640, 1540, 1480 cm^{-1}
ES-MS : 496(M+1)$^+$

Example 80 : Synthesis of 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoic acid (Compound 127)

122㎎ of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate was treated according to the same procedure as Example 44 to obtain 89㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.59-7.28(m, 2H), 6.38(s, 1H), 4.23-4.07(m, 3H), 3.62-3.50(m, 3H), 3.11(m, 1H), 2.77(m, 2H), 2.57-1.61(m, 18H), 1.28(t, 3H, J=7.14Hz)
IR(KBr) : 3400, 3000, 1700, 1640, 1540, 1480 cm^{-1}
ES-MS : 468(M+1)$^+$

Example 81 : Synthesis of ethyl 5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate

(Compound 128)

a) Synthesis of ethyl 5-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate:

138㎎ of the compound II-a obtained in Example 57-b) and 0.066 ㎖ of ethyl 5-bromovalerate were reacted according to the same procedure as Example 45-b) to obtain 150㎎ of the title compound as a brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.62-7.54(m, 2H), 6.46(s, 1H), 4.30-4.04(m, 5H), 3.68-3.51(m, 2H), 3.27-3.16(m, 2H), 2.80(t, 2H, J=7.91Hz), 2.69-1.59(m, 19H), 1.36(t, 3H, J=7.20Hz), 1.20(t, 3H, J=7.13Hz)

b) Synthesis of ethyl 5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate:

246㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 48㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.78(s, 2H), 7.54-7.30(m, 2H), 6.37(s, 1H), 4.22-3.91(m, 5H), 3.60-3.47(m, 2H), 3.19-3.05(m, 2H), 2.81-2.73 (m, 2H), 2.52-1.37(m, 19H), 1.30(t, 3H, J=7.15Hz), 1.05(t, 3H, J=7.88Hz)

IR(KBr) : 3100, 2990, 1740, 1670, 1630, 1530, 1470 cm^{-1}

ES-MS : 510$(M+1)^+$

Example 82 : Synthesis of 5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoic acid (Compound 129)

38㎎ of ethyl 5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate was treated according to the same procedure as Example 44 to obtain 16㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.54-7.29(m, 2H), 6.36(s, 1H), 4.27-4.10(m, 3H), 3.65-3.42(m, 2H), 3.19-3.03(m, 2H), 2.82-2.71 (m, 2H), 2.57-1.41(m, 19H), 1.29(t, 3H, J=7.19Hz)

ES-MS : 482(M+1)$^+$

Example 83 : Synthesis of ethyl 6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate (Compound 130)

a) Synthesis of ethyl 6-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

160㎎ of the compound II-a obtained in Example 57-b) and 0.086 ㎖ of ethyl 6-bromohexanoate were reacted according to the same procedure as Example 45-b) to obtain 168㎎ of the title compound as a brown oil.

^{1}II NMR($CDCl_3$, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.45(s, 1H), 4.27(brs, 1H), 4.18-4.04(m, 4H), 3.68-3.52(m, 2H), 3.26-3.17(m, 2H), 2.80(t, 2H, J=7.95Hz), 2.23(t, 2H, J=7.45Hz), 2.66-1.25(m, 19H), 1.36(t, 3H, J=7.18Hz), 1.21(t, 3H, J=7.13Hz)

b) Synthesis of ethyl 6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

161㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 41㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.78(s, 2H), 7.54-7.30(m, 2H), 6.36(s, 1H), 4.26-3.88(m, 5H), 3.61-3.46(m, 2H), 3.19-3.03(m, 2H), 2.81-2.72 (m, 2H), 2.52-1.38(m, 2H), 1.18(t, 3H, J=7.18Hz), 1.06(t, 3H, J=7.12Hz)

IR(KBr) : 3200, 2970, 1730, 1630, 1530, 1470, 1340 cm^{-1}

ES-MS : 524(M+1)$^+$

Example 84 : Synthesis of 6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoic acid (Compound 131)

30㎎ of ethyl 6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate was treated according to the same procedure as Example 44 to obtain 26㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.54-7.29(m, 2H), 6.34(s, 1H), 4.27-4.11(m, 3H), 3.66-3.45(m, 2H), 3.18-3.04(m, 2H), 2.82-2.71 (m, 2H), 2.50-1.17(m, 21H), 1.28(t, 3H, J=7.15Hz)

ES-MS : 496$(M+1)^+$

Example 85 : Synthesis of ethyl 2-[(R,R)-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidinyl acetate (Compound 135)

a) Synthesis of methyl (R,R)-4-methoxy-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylate:

500㎎ of 4-cis-hydroxy-D-proline was dissolved in 4㎖ of methanol, and 0.4㎖ of acetyl chloride was added dropwise at 0℃. 0.14 ㎖ of thionyl chloride was added dropwise at room temperature, and the resulting mixture was heated under refluxing for 2 hours with stirring. The reaction solution was cooled to room temperature and then evaporated under reduced pressure to obtain 704㎎ of the white solid product, which was then dissolved in 10㎖ of dichloromethane. To the resulting solution was added dropwise 1.07㎖ of triethylamine at 0℃ and then added 930㎎ of $(BOC)_2O$. The reaction mixture was stirred for 2.5 hours at room temperature, diluted with 150㎖ of dichloromethane, washed with 30㎖ of 2N-HCl solution and 30㎖ of water, dried over sodium sulfate and then filtered. The filtrate was then evaporated under reduced pressure to obtain 780㎎ of the brown solid, which was dissolved in 15㎖ of anhydrous tetrahydrofuran. To the resulting solution was

then added 138㎎ of NaH, and the mixture was stirred for one hour at room temperature. 0.214㎖ of methyliodide was slowly added dropwise thereto, and the reaction mixture was heated under refluxing overnight with stirring. After 1㎖ of water was added dropwise, the reaction solution was evaporated under reduced pressure to obtain the residue, which was then diluted with 150㎖ of dichloromethane, washed with 50㎖ of water, dried over sodium sulfate and then filtered. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 404㎎ of the title compound as a viscous oil.

^{1}H NMR($CDCl_3$, ppm) : δ 4.46-4.28(m, 1H), 3.94(brs, 1H), 3.73(s, 3H), 3.63-3.49(m, 2H), 3.30(d, 3H, J=9.48Hz), 2.41-2.22(m, 1H), 2.11-1.98(m, 1H), 1.44(m, 9H)

b) Synthesis of (R,R)-4-methoxy-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid:

520㎎ of the compound obtained in the above a) was reacted in the presence of methanol solvent under the same conditions as Example 44 to obtain 480㎎ of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 4.47-4.34(m, 1H), 3.97(brs, 1H), 3.64-3.49(m, 2H), 3.33(s, 3H), 2.44-2.10(m, 2H), 1.49-1.42(m, 9H)

c) Synthesis of tert-butyl (R,R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidine carboxylate:

203㎎ of the compound I-a obtained in Example 1-l) was reacted with the compound obtained in the above b) according to the same procedure as Example 11-a) to obtain 212㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58-7.52(m, 2H), 7.30(m, 1H), 6.39(m, 1H), 4.31 (m, 1H), 4.21-4.10(m, 2H), 3.97-3.40(m, 6H), 3.32(s, 3H), 2.88-

2.76(m, 2H), 2.58-1.67(m, 8H), 1.45-1.40(m, 9H), 1.35(t, 3H, J=7.11Hz)

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[((R,R)-4-methoxypyrrolidin-2-yl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

210㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-l) to obtain 145㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.59-7.54(m, 2H), 7.29(m, 1H), 6.40(s, 1H), 4.28 (brs, 1H), 4.18-4.10(m, 2H), 4.04-3.93(m, 2H), 3.67-3.42(m, 2H), 3.31(s, 3H), 3.21(s, 1H), 3.00-2.92(m, 1H), 2.85-2.74(m, 2H), 2.43-1.72(m, 9H), 1.36(t, 3H, J=7.19Hz)

e) Synthesis of ethyl-2-[(R,R)-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

98㎎ of the compound obtained in the above d) was reacted with 30㎕ of ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 93㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58-7.53(m, 2H), 7.29(m, 1H), 6.42(s, 1H), 4.31 (brs, 1H), 4.20-4.11(m, 4H), 4.08-4.01(m, 2H), 3.62-3.50(m, 5H), 3.29(s, 3H), 2.82-2.73(m, 3H), 2.35-1.59(m, 8H), 1.35(t, 3H, J=7.24Hz), 1.26(t, 3H, J=7.13Hz)

f) Synthesis of ethyl 2-[(R,R)-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

93㎎ of the compound obtained in the above e) was treated according to the same procedure as Example 1-n) to obtain 16㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.83(s, 1H), 7.54-7.31(m, 2H), 6.38(s, 1H), 4.21-3.85(m, 7H), 3.58-3.29(m, 5H), 3.18(s, 3H), 2.82-2.73(m,

2H), 2.61(m, 1H), 2.19-1.66(m, 8H), 1.29(t, 3H, J=6.85Hz), 1.17-1.08(m, 3H)

ES-MS : 498$(M+1)^+$

Example 86 : Synthesis of ethyl-2-[(R,R)-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate (Compound 136)

a) Synthesis of (R,R)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

0.81g of (R,R)-4-hydroxypyrrolidine-2-carboxylic acid was treated according to the same procedure as Example 66-a) to obtain 1g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.31(m, 5H), 5.19(m, 2H), 4.53(m, 1H), 4.43(m, 1H), 3.60(m, 2H), 2.24(m, 2H)

b) Synthesis of (R,R)-4-methoxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

1g of the compound obtained in the above a) was treated according to the same procedure as Example 66-d) to obtain 1.1g of the title compound as a pale brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.31(m, 5H), 5.16(m, 2H), 4.45(m, 1H), 3.95(m, 1H), 3.64(m, 2H), 3.26(s, 3H), 2.45-2.38(m, 1H), 2.24(m, 1H)

c) Synthesis of phenylmethyl-2-(R,R)-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]piperidinyl]carbonyl]-4-methoxypyrrolidine carboxylate:

0.92g of 1-ethyl-2-[2-((S)-2-piperidyl)ethyl]indole-6-carbonitrile and 1.1g of (R,R)-4-methoxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid were treated according to the same procedure as Example 11-a) to obtain 500㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.35(m, 5H), 7.27(m, 1H), 6.33(s, 1H), 5.09(m, 2H), 4.16(m, 1H), 3.95(m, 2H), 3.66(m, 2H), 3.26(m, 3H), 2.32(m, 2H), 1.41(m, 2H), 1.25(m, 3H)

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[((R,R)-4-methoxypyrrolidin-2-yl)-carbonyl]piperidin-2-yl]ethyl]indole-6-carbonitrile:

480㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-k) to obtain 270㎎ of the title compound as a pale yellow solid.

e) Synthesis of ethyl 2-[(R,R)-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]piperidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

250㎎ of the compound obtained in the above d) and 0.1㎖ of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obtain 200㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.78(m, 1H), 7.54(m, 1H), 7.33(m, 1H), 6.31(s, 1H), 4.95(br, 1H), 4.12(m, 4H), 3.97(m, 2H), 3.72-3.60(m, 2H), 3.28(m, 3H), 3.02(m, 1H), 2.71(m, 1H), 2.61-2.49(m, 2H), 2.19(m, 1H), 1.30(m, 3H), 1.26-1.19(m, 6H)

f) Synthesis of ethyl 2-[(R,R)-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]piperidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

190㎎ of the compound obtained in the above e) was treated according to the same procedure as Example 1-n) to obtain 50㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.77(m, 1H), 7.54(m, 1H), 7.33(m, 1H), 6.31(s, 1H), 4.95(br, 1H), 4.15(m, 4H), 3.98-3.87(m, 2H), 3.62(m, 2H), 3.28(m, 3H), 3.05(m, 1H), 2.70(m, 1H), 2.77-2.52(m, 2H), 2.18(br, 1H), 1.84(m, 2H), 1.67(m, 5H), 1.32(m, 3H), 1.24(m, 3H)

IR(KBr) : 3400, 2920, 1720, 1630, 1460 cm^{-1}

ES-MS : 512(M+1)$^+$

Example 87 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-hydroxyethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 140)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-hydroxyethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

130㎎ of the compound II-a obtained in Example 57-b) and 0.1㎖ of 2-bromoethanol were treated according to the same procedure as Example 45-b) to obtain 140㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : 7.50(m, 2H), 7.25(s, 1H), 6.34(s, 1H), 4.20(m, 1H), 4.10(t, 3H), 3.52(m, 2H), 3.37(m, 2H), 3.21(m, 2H), 2.76(m, 2H), 2.44(m, 2H), 2.32-1.60(m, 11H), 1.27(t, 3H)

ES-MS : 409(M+1)$^+$

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-hydroxyethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

140㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 45㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.58(m, 1H), 7.34(s, 1H), 6.83(d, 1H), 4.20(m, 1H), 4.05(s, 3H), 3.57(m, 2H), 3.60(m, 2H), 3.47(m, 2H), 3.20(m, 2H), 2.83(m, 2H), 2.65(m, 2H), 2.40-1.80(m, 11H), 1.37(m, 3H)

ES-MS : 426(M+1)$^+$

Example 88 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 142)

a) Synthesis of N-[2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-oxoethyl]-N-methyl-(tert-butoxy)formamide:

101㎎ of the compound II-a obtained in Example 57-b) and 52㎎ of N-(tert-butoxycarbonyl)sarcosine were reacted according to the same procedure as Example 11-a) to obtain 106㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.52(m, 2H), 7.27(m, 1H), 6.34(s, 1H), 4.67 (m, 1H), 4.28-4.12(m, 3H), 3.81-3.44(m, 6H), 2.88(s, 3H), 2.79(t, 2H, J=7.90Hz), 2.28-1.73(m, 10H), 1.44(s, 9H), 1.35(t, 3H, J=7.31Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

103㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 46㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.55-7.31(m, 2H), 6.37(s, 1H), 4.57(m, 1H), 4.22-4.08(m, 3H), 3.75-3.47(m, 4H), 3.31(s, 2H), 2.77(brs, 2H), 2.27(s, 3H), 2.19-1.77(m, 10H), 1.29(t, 3H, J=7.12Hz)

IR(KBr) : 3440, 1640, 1025 cm^{-1}

ES-MS : 453(M+1)$^+$

Example 89 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-aminopropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 143)

a) Synthesis of N-[(1S)-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-1-methyl-2-oxoethyl]-(tert-butoxy)formamide:

300㎎ of the compound II-a obtained in Example 57-b) and 187㎎ of (S)-2-[(tert-butoxy)carbonylamino]propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 210㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.24(m, 1H), 6.35(s, 1H), 4.57(m, 1H), 4.49(m, 1H), 4.32(m, 1H), 4.13(m, 2H), 3.79(m, 2H), 3.58-3.43(br, 2H), 2.81(m, 2H), 2.12(m, 4H), 1.42(m, 9H), 1.35(m, 6H)
ES-MS : 356(M+1)$^+$

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-aminopropanoyl)-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

200㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 100㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(m, 1H), 7.38(m, 1H), 7.23(m, 1H), 6.15(m, 1H), 4.57(m, 2H), 4.13(br, 3H), 3.83(m, 2H), 3.66(m, 1H), 3.45(m, 2H), 2.71(m, 2H), 2.12(m, 3H), 1.97-1.84(br, 6H), 1.25-1.17(m, 6H)
IR(KBr) : 3420, 3000, 1640 cm^{-1}
ES-MS : 453(M+1)$^+$

Example 90 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-amino-butanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 144)

a) Synthesis of N-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-1-ethyl-2-oxoethyl](tert-butoxy) formamide:

400㎎ of the compound II-a obtained in Example 57-b) and 270㎎ of 3-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 350㎎ of the title

compound as a yellow oil.

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-aminobutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

340㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 190㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.83(m, 1H), 7.32(m, 1H), 7.16(m, 1H), 6.21(s, 1H), 4.60(m, 2H), 4.18(m, 5H), 3.88(m, 2H), 3.78(m, 2H), 3.64(m, 1H), 3.48(m, 5H), 2.72(m, 3H), 2.16(m, 5H), 1.24(m, 5H), 0.95(m, 3H)

IR(KBr) : 3400, 3000, 1640 cm^{-1}

ES-MS : 467(M+1)$^+$

Example 91 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl]cabonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine (Compound 145)

a) Synthesis of N-[(1S)-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-1-isopropyl-2-oxo-ethyl](tert-butoxy)formamide:

250㎎ of the compound II-a obtained in Example 57-b) and 298㎎ of 3-methyl-(S)-2-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 300㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.52(m, 2H), 7.30(m, 1H), 6.32(s, 1H), 5.18(m, 1H), 4.54(m, 1H), 4.23-4.14(m, 1H), 4.15(q, 2H), 3.88(m, 2H), 3.68-3.39(m, 2H) 2.82(m, 2H), 2.71-2.32(m, 10H), 1.38(brs, 9H), 1.34(t, 3H), 0.98(m, 3H), 0.85(m, 4H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-methylbuta-

noyl)pyrrolidin-2-yl]cabonyl]pyrrolidin-2-yl]ethyl]-1-ethylindole-6-car-boxamidine:

140㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 59㎎ of the title compound as a pale yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.69(m, 1H), 7.42(m, 1H), 7.22(m, 1H), 6.28(s, 1H), 4.58(m, 1H), 4.33-4.16(m, 2H), 4.11(q, 2H), 3.91-3.72(m, 2H), 3.58-3.38(m, 2H), 2.73(m, 2H), 2.22-1.77(m, 10H), 1.28(t, 3H), 0.89(m, 7H)

ES-MS : 482$(M+2)^+$

IR(KBr) : 2997, 1642, 1543, 1480 cm^{-1}

Example 92 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 146)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-aminopropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

294㎎ of N-[(S)-2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-1-methyl-2-oxoethyl](tert-butoxy)formamide was treated according to the same procedure as Example 1-l) to obtain 220㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.21(m, 1H), 6.37(s, 1H), 4.58(m, 1H), 4.27(m, 1H), 4.14(q, 2H), 3.82-3.58(m, 3H), 3.42(m, 2H), 2.82(m, 2H), 2.26-1.78(m, 10H), 1.37(t, 3H), 1.21(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

140㎎ of the compound obtained in the above a) and 20㎕ of

methanesulfonyl chloride were reacted according to the same procedure as Example 1-m) to obtain 120㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.59(m, 2H), 7.28(m, 1H), 6.41(s, 1H), 5.13(m, 1H), 4.61(m, 1H), 4.32(m, 1H), 4.14(q, 2H), 3.89-3.75(m, 2H), 3.55-3.48(m, 2H), 2.86(s, 6H), 2.75(m, 2H), 2.28-1.74(m, 10H), 1.38(m, 6H)

ES-MS : 514(M+1)$^+$

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

120㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 61㎎ of the title compound as a pale yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.94(m, 1H), 7.41(m, 1H), 7.23(m, 1H), 6.22(s, 1H), 4.61(m, 1H), 4.35(m, 1H), 4.18(m, 3H), 3.92-3.75(m, 2H), 3.56-3.38(m, 2H), 2.86(s, 3H), 2.68(m, 2H), 2.22-1.71(m, 10H), 1.42(t, 3H), 1.24(m, 3H)

ES-MS : 531(M+1)$^+$

IR(KBr) : 2998, 1643, 1541, 1342 cm^{-1}

Example 93 : Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoate (Compound 147)

a) Synthesis of phenylmethyl-4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-3-[(tert-butoxy)carbonylamino]-4-oxobutanoate:

0.6g of the compound II-a obtained in Example 57-b) and 798㎎ of (S)-2-[(tert-butoxy)carbonylamino]-3-(benzyloxycarbonyl)propanoic

acid were reacted according to the same procedure as Example 11-a) to obtain 1.1g of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.52(m, 2H), 7.35-7.17(m, 6H), 6.33(s, 1H), 5.26 (m, 1H), 4.98(m, 2H), 4.88(m, 1H), 4.47(m, 1H), 4.12(q, 2H), 3.78-3.39(m, 4H), 2.88-2.66(m, 4H), 2.23-1.71(m, 10H), 1.39(brs, 9H), 1.29(t, 3H)

ES-MS : 682($M+Na^+$), 670$(M+1)^+$

b) Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoate:

1.1g of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 250mg of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(m, 1H), 7.39(m, 1H), 7.22(m, 1H), 6.27(s, 1H), 4.66-4.47(m, 1H), 4.27-3.95(m, 6H), 3.86-3.37(m, 4H), 2.79-2.42(m, 4H), 2.19-1.73(m, 10H), 1.31-1.19(m, 6H)

ES-MS : 525$(M+1)^+$

IR(KBr) : 3028, 1768, 1647, 1374 cm^{-1}

Example 94 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-carbamoylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 148)

1.1g of phenylmethyl-4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-3-[(tert-butoxy)carbonyl-amino]-4-oxobutanoate was treated according to the same procedure as Example 1-n) to obtain 150mg of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.77(m, 1H), 7.48(m, 1H), 7.32(m, 1H), 6.34(s, 1H), 4.49(m, 1H), 4.22-4.07(m, 3H), 3.92(m, 1H), 3.66(m, 2H), 3.38(m, 2H), 2.71(m, 2H), 2.50-2.25(m, 2H), 2.22-1.74(m, 10H), 1.30(t, 3H)

ES-MS : 496(M+1)$^+$

IR : 3086, 1637, 1367 cm^{-1}

Example 95 : Synthesis of 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoic acid (Compound 149)

150mg of ethyl-4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(3S)-3-amino-4-oxobutanoate and 50mg of 2-[2-[(S)-1-[[(R)-1-[((S)-2-amino-3-carbamoyl)propanoyl]-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-1-ethylindole-6-carboxami-dine were reacted under the same conditions as Example 44 to obtain 145mg of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.75(m, 1H), 7.51(m, 1H), 7.30(m, 1H), 6.32 (s, 1H), 4.56-4.28(m, 1H), 4.21-4.08(m, 3H), 3.93(m, 1H), 3.81-3.66(m, 2H), 3.52-3.25(m, 2H), 2.76(m, 2H), 2.54-2.18(m, 2H), 2.12-1.69(m, 10H), 1.28(t, 3H)

ES-MS : 498(M+2)$^+$

IR(KBr) : 1632, 1372 cm^{-1}

Example 96 : Synthesis of 1-ethyl-2-[2-[((S)-1-[[(R)-1-(3-amino-propanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 155)

a) Synthesis of 2-[2-[(S)-1-[[(R)-1-(3-chloropropanoyl)pyrrolidin-2-yl]-carbonyl]pyrrolidin-2-yl]ethyl]-1-ethylindole-6-carbonitrile:

800mg of the compound II-a obtained in Example 57-b) and 0.475 mℓ of 3-chloropropionic acid were reacted according to the same procedure as Example 11-a) to obtain 926mg of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61(s, 1H), 7.56(d, 1H, J=8.81Hz), 7.26(d, 1H, J=8.98Hz), 6.37(s, 1H), 4.65(m, 1H), 4.28(m, 1H), 4.15(q, 2H), 3.82 (m, 2H), 3.71(m, 4H), 3.62-3.40(m, 2H), 2.78(m, 4H), 2.30-1.78

(m, 10H), 1.33(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

320㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 98㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.92(s, 1H), 7.65(d, 1H, J=8.25Hz), 7.46(d, 1H), 6.49(s, 1H), 4.40-4.16(m, 3H), 3.87(m, 1H), 3.78-3.53(m, 4H), 2.91(m, 4H), 2.89(m, 2H), 2.40-1.80(m, 10H), 1.41(t, 3H)

Example 97 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 156)

a) Synthesis of N-[3-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-methyl-3-oxopropyl](tert-butoxy)formamide:

430㎎ of the compound II-a obtained in Example 57-b) and 290㎎ of 2-methyl-3-[(tert-butoxy)carbonylamino]propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 270㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.57(m, 2H), 7.28(m, 1H), 6.36(d, 1H), 4.62(m, 1H), 4.26(m, 1H), 4.16(m, 2H), 3.47(m, 2H), 3.22(m, 2H), 2.79(m, 2H), 2.15(m, 3H), 1.93(m, 6H), 1.60(m, 9H), 1.27(m, 3H), 1.12(t, 3H)

ES-MS : 550(M+1)$^+$, 573(M+Na)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine

250㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 100㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.89(d, 1H, J=7.00Hz), 7.32(m, 1H), 7.18(m, 1H), 6.19(d, 1H, J=8.70Hz), 4.61(m, 1H), 4.14(m, 2H), 3.85(m, 3H), 3.45(m, 2H), 2.69(m, 2H), 2.19(m, 6H), 1.26(m, 5H), 1.07(m, 3H), 1.02(m, 3H)

IR(KBr) : 3420, 1650 cm^{-1}

ES-MS : 467(M+1)$^+$

Example 98 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-amino-butanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 157)

a) Synthesis of N-[3-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-1-methyl-3-oxopropyl](tert-butoxy)formamide:

430㎎ of the compound II-a obtained in Example 57-b) and 290㎎ of 3-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 260㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.57(m, 2H), 7.29(m, 1H), 6.36(s, 1H), 4.62(m, 1H), 4.15(t, 2H, J=7.20Hz), 4.03(m, 1H), 3.69(m, 2H), 3.47(m, 3H), 2.80(m, 2H), 2.57(m, 2H), 2.16(m, 3H), 1.93(m, 6H), 1.43(m, 9H), 1.37(m, 3H), 1.20(m, 3H)

ES-MS : 550(M+1)$^+$

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-aminobutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

250㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 110㎎ of the

title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.87(m, 1H), 7.35(m, 1H), 7.20(m, 1H), 6.21(s, 1H), 4.60(m, 1H), 4.21(m, 4H), 3.85(m, 2H), 2.72(m, 3H), 2.11(br, 6H), 1.98(br, 3H), 1.21(m, 3H), 1.04(m, 3H)

IR(KBr) : 3400, 2840, 1650, 1020 cm^{-1}

ES-MS : 467(M+1)$^+$

Example 99 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 158)

a) Synthesis of N-[3-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropyl](tert-butoxy)formamide

500㎎ of the compound II-a obtained in Example 57-b) and 290㎎ of 3-[(tert-butoxy)carbonylamino]propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 340㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.26(m, 1H), 6.37(s, 1H), 4.63(m, 1H), 4.28(m,1H), 4.15(t, 2H, J=7.20Hz), 3.81(m, 1H), 3.66(m, 2H), 3.41(m, 6H), 2.80(m, 2H), 2.52(m, 2H), 2.18(m, 4H), 1.98(m, 6H), 1.42(m, 9H), 1.32(m, 3H)

ES-MS : 536(M+1)$^+$, 558(M+Na), 574(M+K)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

340㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 160㎎ of the title compound as a yellow oil.

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[3-[(methanesulfonyl)amino]-propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbo-

nitrile:

180㎎ of the compound obtained in the above b) and 55㎕ of methanesulfonyl chloride were reacted according to the same procedure as Example 1-m) to obtain 100㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.25(m, 1H), 6.41(s, 1H), 4.62(m, 1H), 4.24(m, 1H), 4.18(t, 2H, J=7.20Hz), 3.75(m, 2H), 3.48-3.39(m, 4H), 2.87-2.79(m, 4H), 2.20(m, 2H), 2.01-1.90(br, 7H), 1.35(m, 3H)

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[3-[(methanesulfonyl)amino]-propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

100㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 60㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.69(s, 1H), 7.54(m, 1H), 7.28(m, 1H), 6.34(s, 1H), 4.60(m, 1H), 4.21(m, 3H), 3.73(m, 2H), 3.34(m, 2H), 2.83(s, 3H), 2.79(m, 2H), 2.16(m, 4H), 2.02-1.96(br, 4H), 1.33(t, 3H, J=7.10Hz)

IR(KBr) : 3300, 3000, 1640 cm^{-1}

ES-MS : 531(M+1)$^+$

Example 100 : Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoate (Compound 159)

a) Synthesis of phenylmethyl-4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-[(*tert*-butoxy)carbonylamino]-4-oxobutanoate:

0.6g of the compound II-a obtained in Example 57-b) and 0.798g

of (S)-3-[(tert-butoxy)carbonylamino]-3-(benzyloxycarbonyl)propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 1.08g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.51(m, 1H), 7.49(m, 1H), 7.32-7.04(m, 6H), 6.30 (s, 1H), 5.67(m, 1H), 4.86-4.72(m, 2H), 4.59-4.46(m, 1H), 4.27-4.01(m, 3H), 3.83-3.58(m, 2H), 3.46-3.37(m, 2H), 3.09-2.66(m, 4H), 2.27-1.69(m, 10H), 1.42(brs, 9H), 1.25(t, 3H)

ES-MS : 692($M+Na^+$), 670$(M+1)^+$

b) Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoate:

1.08g of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 250㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.77(m, 1H), 7.44(m, 1H), 7.28(m, 1H), 6.28(s, 1H), 4.62(m, 1H), 4.21(m, 4H), 4.06(q, 2H), 3.90-3.71(m, 2H), 3.61-3.39(m, 2H), 2.71(m, 4H), 2.28-1.72(m, 10H), 1.32(t, 3H), 1.18(t, 3H)

ES-MS : 525$(M+1)^+$

IR(KBr) : 1752, 1648, 1375 cm^{-1}

Example 101 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 160)

1.08g of phenylmethyl 4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-[(tert-butoxy)carbo-nylamino]-4-oxobutanoate was treated according to the same procedure as Example 1-n) to obtain 230㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4) : δ 7.78(m, 1H), 7.49(m, 1H), 7.28(m, 1H), 6.35(s, 1H), 4.53(m, 1H), 4.19-4.08(m, 3H), 3.76-3.38(m, 5H), 2.81-2.42(m,

4H), 2.25-1.71(m, 10H), 1.28(t, 3H)
ES-MS : 496(M+1)$^+$
IR(KBr) : 3098, 1641, 1498, 1365 cm^{-1}

Example 102 : Synthesis of 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoic acid (Compound 161)

170mg of ethyl-4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoate and 130mg of 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine were reacted under the same conditions as Example 44 to obtain 170 mg of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.75(m, 1H), 7.46(m, 1H), 7.25(m, 1H), 6.31 (s, 1H), 4.52(m, 1H), 4.18-4.05(m, 3H), 3.77-3.38(m, 5H), 2.89-2.39(m, 4H), 2.29-1.70(m, 10H), 1.26(t, 3H)
ES-MS : 498(M+2)$^+$
IR(KBr) : 2980, 1615, 1459, 1381 cm^{-1}

Example 103 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 162)

a) Synthesis of phenylmethyl 4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-[(tert-butoxy)carbonylamino]-4-oxobutanoate:

0.3g of the compound II-a obtained in Example 57-b) and 0.346g of (S)-3-[(tert-butoxy)carbonylamino]-3-(benzyloxycarbonyl)propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 0.54g of the title compound as a pale yellow solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 7.71(m, 1H), 7.49(m, 1H), 7.32-7.04(m, 6H), 6.30(s, 1H), 5.67(m, 1H), 4.86-4.72(m, 2H), 4.59-4.46(m, 1H), 4.27-4.01(m, 3H), 3.83-3.58(m, 2H), 3.46-3.37(m, 2H), 3.09-2.66 (m, 4H), 2.27-1.69(m, 10H), 1.42(brs, 9H), 1.25(t, 3H)

ES-MS : 692(M+Na$^+$), 670(M+1)$^+$

b) Synthesis of phenylmethyl 2-amino-4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate:

0.53g of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 0.40g of the title compound as a pale yellow solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 7.58(m, 2H), 7.40-7.21(m, 6H), 6.32(s, 1H), 5.08 -4.96(m, 2H), 4.67-4.48(m, 1H), 4.28-4.08(m, 3H), 3.86-3.67(m, 3H), 3.59-3.38(m, 2H), 2.78(m, 4H), 2.30-1.76(m, 10H), 1.34(t, 3H)

ES-MS : 570(M+1)$^+$

c) Synthesis of phenylmethyl 4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-[(methylsulfonyl)-amino]-4-oxobutanoate:

395㎎ of the compound obtained in the above b) and 0.08㎖ of methanesulfonyl chloride were reacted according to the same procedure as Example 1-m) to obtain 300㎎ of the title compound as a pale yellow solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 7.51(m, 1H), 7.45(m, 1H), 7.39(m, 1H), 7.29(m, 3H), 7.10(m, 2H), 6.31(s, 1H), 5.73(m, 1H), 4.87-4.69(m, 2H), 4.63-4.45(m, 1H), 4.29-4.06(m, 3H), 3.26-3.19(m, 1H), 2.96(s, 3H), 2.90-2.67(m, 3H), 2.30-1.79(m, 10H), 1.33(t, 3H)

ES-MS : 670(M+Na$^+$), 648(M+1)$^+$

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-

[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

300㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 25㎎ of the title compound as a pale yellow solid.

^{1}H-NMR(MeOH-d_4, ppm) : δ 7.76(m, 1H), 7.49(m, 1H), 7.28(m, 1H), 6.34(s, 1H), 4.53(m, 1H), 4.25-4.09(m, 4H), 3.75-3.38(m, 4H), 2.85-2.61(m, 4H), 2.55(s, 3H) 2.26-1.69(m, 10H), 1.28(t, 3H)
ES-MS : 574(M+1)$^+$
IR(KBr) : 2993, 2385, 1681, 1632, 1472, 1389 cm^{-1}

Example 104 : Synthesis of 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-(S)-2-[(methanesulfonyl)amino]-4-oxobutanoic acid (Compound 163)

60㎎ of 1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine obtained in Example 103 was treated according to the same procedure as Example 44 to obtain 15㎎ of the title compound as a pale yellow solid.

^{1}H-NMR(MeOH-d_4, ppm) : δ 7.86(m, 1H), 7.52(m, 1H), 7.34(m, 1H), 6.36 (s, 1H), 4.53(m, 1H), 4.28-4.10(m, 4H), 3.77-3.39(m, 4H), 2.87-2.56(m, 7H), 2.24-1.68(m, 10H), 1.32(t, 3H)
ES-MS : 575(M+1)$^+$
IR(KBr) : 2998, 1628, 1468, 1332 cm^{-1}

Example 105 : Example of 1-ethyl-2-[2-[(S)-1-[[(R)-(1-(4-amino-butanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 166)

a) Synthesis of 1-[4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutyl](tert-butoxy)formamide:

400㎎ of the compound II-a obtained in Example 57-b) and 270㎎ of 4-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 360㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(m, 2H), 7.26(m, 1H), 6.37(s, 1H), 4.63(m, 1H), 4.28(m, 1H), 4.15(t, 2H, J=7.20Hz), 3.82(m, 1H), 3.66(m, 2H), 3.46(m, 3H), 2.80(m, 4H), 2.52(m, 2H), 2.17(m, 4H), 1.91(m, 2H), 1.42(m, 9H), 1.35(m, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(4-aminobutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

350㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 170㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.92(m, 1H), 7.34(m, 2H), 6.19(s, 1H), 4.55(m, 1H), 4.16(m, 3H), 3.78(m, 1H), 3.62(m, 2H), 3.41(m, 3H), 2.62(m, 4H), 2.30(m, 2H), 2.07(m, 3H), 1.68(m, 4H), 1.24(m, 3H)

IR(KBr) : 3400, 3000, 1630 cm^{-1}

ES-MS : 467(M+1)$^+$

Example 106 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(2-piperidinyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 167)

a) Synthesis of tert-butyl-2-[[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]carbonyl]piperidine carboxylate:

400㎎ of the compound II-a obtained in Example 57-b) and 300㎎ of 1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 350㎎ of the

title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.57(m, 2H), 7.26(m, 1H), 6.35(m, 1H), 4.66(m, 1H), 4.24(m, 1H), 4.14(m, 2H), 3.87(m, 2H), 3.48(m, 2H), 2.80(m, 2H), 2.15(m, 3H), 2.04-1.92(br, 7H), 1.46(m, 9H), 1.35(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(2-piperidyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

330㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 200㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.62(m, 1H), 7.48(m, 1H), 7.21(m, 1H), 6.32(m, 1H), 4.59(m, 1H), 4.19(m, 4H), 3.85(m, 2H), 3.71(m, 2H), 3.4(m, 3H), 3.12(m, 2H), 2.76(t, 2H), 2.29-2.08(br, 3H), 1.81-1.65(br, 5H), 1.39-1.29(br, 5H), 1.23(m, 3H)

IR(KBr) : 3400, 2880, 1640 cm^{-1}

ES-MS : 493(M+1)$^+$

Example 107 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 168)

a) Synthesis of tert-butyl 3-[[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]carbonyl]piperidinecarboxylate:

300㎎ of the compound II-a obtained in Example 57-b) and 226㎎ of 1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 380㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.54(m, 2H), 7.24(m, 1H), 6.36(s, 1H), 4.60(m, 1H), 4.26(m, 1H), 4.15(m, 3H), 3.84(m, 2H), 3.71(m, 1H), 3.60(m, 1H), 3.47(m, 1H), 2.80(m, 3H), 2.17(m, 2H), 2.07-1.90(br, 4H),

1.45(m, 9H), 1.35(m, 3H)
ES-MS : 576(M+1)$^+$, 598(M+Na)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

350㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 210㎎ of the title compound as a yellowish white solid.

IR(KBr) : 3400, 2880, 1640 cm^{-1}
ES-MS : 493(M+1)$^+$

Example 108 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 169)

a) Synthesis of tert-butyl 4-[[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]carbonyl]piperidine carboxylate:

300㎎ of the compound II-a obtained in Example 57-b) and 226㎎ of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 200㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.26(m, 1H), 6.38(s, 1H), 4.54(m, 1H), 4.23(m, 1H), 4.12(m, 3H), 3.80(m, 2H), 3.72(m, 1H), 3.51(m, 2H), 2.79(m, 4H), 2.55(m, 1H), 2.30-2.14(br, 3H), 2.01-1.92(br, 6H), 1.75-1.66(br, 5H), 1.44(m, 9H), 1.32(m, 3H)
ES-MS : 576(M+1)$^+$, 598(M+Na)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-[(4-piperidinyl)carbonyl]-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

170㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 100㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.84(m, 1H), 7.46(m, 1H), 7.21(m, 1H), 6.25(m, 1H), 4.58(m, 1H), 4.34(m, 2H), 4.16(m, 2H), 3.71(m, 1H), 3.56(m, 2H), 3.12(m, 1H), 2.63(m, 1H), 2.57(m, 3H), 2.05(m, 2H), 1.99(m, 3H), 1.62-1.55(br, 3H), 1.25(m, 3H)

IR(KBr) : 3400, 3000, 1640 cm^{-1}

ES-MS : 493(M+1)$^+$

Example 109 : Synthesis of 1-methyl-2-[2-[(S)-1-[((R)-1-acetyl-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 170)

a) Synthesis of 1-methyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

90㎎ of the compound II-b obtained in Example 58-a) was dissolved in dichloromethane and the resulting solution was cooled to -78 ℃. 182㎕ of triethylamine was added thereto and after 20 minutes, 356 ㎕ of acetyl chloride was added dropwise. After 20 minutes, water was added and the reaction solution was extracted twice with dichloromethane. The extracts were combined, dried over $MgSO_4$ amd then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 69㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.68(s, 1H), 7.45(d, 1H), 7.14(d, 1H), 6.32(s, 1H), 4.45(m, 1H), 4.09(m, 1H), 3.80(s, 3H), 3.44(m, 2H), 2.70(m, 2H), 1.97(s, 3H), 2.20-1.65(m, 12H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

210㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 117㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.88(s, 1H), 7.59(d, 1H), 7.44(d, 1H), 6.46(s, 1H), 4.65-4.57(m, 1H), 4.25-4.15(m, 1H), 3.80(s, 3H), 3.62(m, 2H), 2.88(m, 2H), 2.11(s, 3H), 2.35-1.80(m, 12H)

Example 110 : Synthesis of 1-ethyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 171)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

45㎎ of the compound II-a obtained in Example 57-b) was dissolved in dichloromethane and the resulting solution was cooled to -78 ℃. 34㎕ of triethylamine was added thereto and after 20 minutes, 18㎕ of acetyl chloride was added dropwise. After 20 minutes, water was added and the reaction solution was extracted three times with dichloromethane. The extracts were combined, dried over $MgSO_4$ amd then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 38㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60-7.48(m, 2H), 7.27(s, 1H), 6.36(s, 1H), 4.57 (t, 1H), 4.25(bs, 1H), 4.20-4.08(m, 1H), 3.55-3.36(m, 2H), 2.80(t, 2H), 2.09(s, 3H), 2.40-1.70(m, 12H), 1.34(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

800㎎ of the compound obtained in the above a) was dissolved in 30㎖ of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for 2 days at room temperature and then

concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vaccum pump. The dried product was then dissolved in 30㎖ of ethanol solution saturated with NH_3 gas. After 2 days, the resulting solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 467㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.92(s, 1H), 7.65(d, 1H), 7.45(d, 1H), 6.49(s, 1H), 4.62(t, 1H), 4.27(m, 3H), 3.73-3.48(m, 2H), 2.89(t, 2H), 2.10(s, 3H), 2.30-1.80(m, 12H), 1.40(t, 3H)

Example 111 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 173)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

300㎎ of the compound II-a obtained in Example 57-b) and 0.257 ㎖ of 2-propylpentanoic acid were reacted according to the same procedure as Example 11-a) to obtain 380㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65-7.47(m, 2H), 7.25(d, 1H), 6.35(s, 1H), 4.68 (m, 1H), 4.24(m, 2H), 4.14(q, 2H), 3.88(m, 1H), 3.73(m, 1H), 3.56 (m, 1H), 3.41(m, 1H), 2.77(m, 2H), 2.55(m, 1H), 2.37-1.50(m, 10H), 1.43-1.17(m, 11H), 0.87(t, 3H), 0.79(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

380㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 268㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.71(s, 1H), 7.60(d, 1H), 7.25(d, 1H), 6.33(s, 1H), 4.65(m, 1H), 4.21(m, 3H), 3.89(m, 1H), 3.74(m, 1H), 3.60(m, 1H), 3.46(m, 1H), 2.78(m, 2H), 2.54(m, 1H), 2.30-1.50(m, 12H), 1.42-0.92(m, 11H), 0.85(t, 3H), 0.77(t, 3H)

ES-MS : 508(M+1)$^+$

Example 112 : Synthesis of ethyl 3-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate (Compound 174)

a) Synthesis of methyl 3-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate:

600㎎ of the compound II-a obtained in Example 57-b) and 0.353 ㎖ of ethylsuccinyl chloride were reacted according to the same procedure as Example 1-m) to obtain 414㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.52(t, 2H), 7.22(s, 1H), 6.32(s, 1H), 4.65(m, 1H), 4.25(m, 1H), 4.16(q, 2H), 3.72(m, 5H), 3.62(m, 2H), 3.42(m, 3H), 2.77(m, 2H), 2.30-1.80(m, 10H), 1.34(t, 3H)

b) Synthesis of ethyl 3-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate:

300㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 97㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.87(s, 1H), 7.64(d, 1H, J=8.40Hz), 7.44(d, 1H, J=6.67Hz), 6.49(s, 1H), 4.30(m, 3H), 4.18(q, 2H), 3.82(m, 1H), 3.75-3.50(m, 4H), 3.00-2.75(m, 2H), 2.45-1.75(m, 12H), 1.40(t, 3H), 1.20(t, 3H)

ES-MS : 496(M+1)$^+$

Example 113 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-carba-

moylacetyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 175)

300㎎ of methyl 3-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate obtained in Example 112-a) was treated according to the same procedure as Example 1-n) to obtain 64㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81(s, 1H), 7.48(d, 1H), 7.33(d, 1H), 6.36(s, 1H), 4.16(m, 3H), 3.73(m, 1H), 3.56(m, 2H), 3.45(m, 2H), 2.75(m, 2H), 2.29-1.50(m, 12H), 1.23(t, 3H)

Example 114 : Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate (Compound 176)

a) Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate:

300㎎ of the compound II-a obtained in Example 57-b) and 250㎎ of ethyl 3-(chlorocarbonyl)propanoate were reacted according to the same procedure as Example 1-m) to obtain 380㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.82(s, 1H), 7.45(d, 1H, J=8.22Hz), 7.13(d, 1H, J=6.83Hz), 6.32(s, 1H), 4.50(m, 1H), 4.20-3.90(m, 5H), 3.70(m, 1H), 3.56(m, 1H), 3.43(m, 2H), 2.85-2.34(m, 6H), 2.22-1.65(m, 10H), 1.23(t, 3H), 1.13(t, 3H)

b) Synthesis of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate:

380㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 117㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.82(s, 1H), 7.50(d, 1H), 7.40(d, 1H), 6.30(s, 1H), 4.50(m, 1H), 4.30-3.80(m, 5H), 3.67(m, 1H), 3.60-3.30(m, 3H), 2.90-2.35(m, 6H), 2.20-1.70(m, 10H), 1.30-1.05(m, 6H)
ES-MS : 510(M+1)$^+$

Example 115 : Synthesis of 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoic acid (Compound 177)

153㎎ of ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate obtained in Example 114 was treated according to the same procedure as Example 44 to obtain 120㎎ of the title compound as a white foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(s, 1H), 7.40(ddd, 2H, J=8.28Hz, 4.60Hz, 1.61Hz), 6.30(s, 1H), 4.50(m, 1H), 4.10(m, 2H), 3.80-3.30(m, 5H), 2.90-2.55 (m, 2H), 2.55-1.60(m, 14H), 1.25(t, 3H, J=7.14Hz)
ES-MS : 482(M+1)$^+$
IR(KBr) : 3190, 2950, 1620 cm^{-1}

Example 116 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-sulfanylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 178)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-sulfanylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

105㎎ of the compound II-a obtained in Example 57-b) and 28㎕ of 3-sulfanylpropanoic acid were reacted according to the same procedure as Example 11-a) to obtain 42㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.24(m, 3H), 6.37(s, 1H), 4.64(m, 1H), 4.26 (brs, 1H), 4.14(q, 2H, J=6.83Hz), 3.88-3.45(m, 4H), 2.80-2.61(m, 6H), 2.22-1.79(m, 10H), 2.70(t, 3H, J=7.25Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-(1-(3-sulfanylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

42㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 14㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.78(s, 1H), 7.49-7.29(m, 2H), 6.31(s, 1H), 4.51(m, 1H), 4.19-4.08(m, 3H), 3.71-3.34(m, 4H), 2.82-2.50(m, 6H), 2.10-1.71(m, 10H), 1.25(m, 3H)
IR(KBr) : 3400, 3000, 1640, 1480 cm^{-1}
ES-MS : 470(M+1)$^+$

Example 117 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine (Compound 180)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-hydroxybutanpyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

0.5g of the compound II-a obtained in Example 57-b) and 0.4㎖ of 4-hydroxypentanoic acid were reacted according to the same procedure as Example 11-a) to obtain 0.6g of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.51(m, 2H), 7.27(m, 1H), 6.38(s, 1H), 4.66-4.44(m, 1H), 4.37-4.14(m, 3H), 3.89-3.66(m, 2H), 3.59-3.40 (m, 2H), 2.83(m, 2H), 2.59-2.29(m, 3H), 2.24-1.72(m, 10H), 1.38 (t, 3H), 1.22(t, 3H)
ES-MS : 473(M+Na$^+$), 451(M+1)$^+$

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine

0.6g of the compound obtained in the above a) was treated

according to the same procedure as Example 1-n) to obtain 0.6g of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.78(m, 1H), 7.48(m, 1H), 7.29(m, 1H), 6.34 (s, 1H), 4.59-4.35(m, 1H), 4.29-4.07(m, 3H), 3.79-3.41(m, 4H), 2.80(m, 2H), 2.58-2.51(m, 3H), 2.11-1.78(m, 10H), 1.27(t, 3H), 1.10(t, 3H)

ES-MS : 468(M+1)$^+$

IR(KBr) : 3167, 2973, 1614, 1508, 1451, 1322 cm^{-1}

Example 118 : Synthesis of 1-ethyl-2-[2-[(S)-1-[((R)-1-prop-2-enoyl-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 182)

320mg of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-chloropropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 96-a) was treated according to the same procedure as Example 1-n) to obtain 84mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.96(s, 1H), 7.64(d, 1H, J=8.29Hz), 7.44(d, 1H, J=8.38Hz), 6.70(q, 1H), 6.50(s, 1H), 6.29(d, 1H, J=16.85Hz), 5.77(d, 1H, J=12.40Hz), 4.32(m, 3H), 3.70(m, 3H), 3.68(m, 2H), 3.59(m, 2H), 2.90(m, 2H), 2.35-1.80(m, 12H), 1.39(t, 3H)

Example 119 : Synthesis of 1-methyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 183)

a) Synthesis of 1-methyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

80mg of the compound II-b obtained in Example 58-a) was dissolved in dichloromethane, and the resulting solution was cooled to -78 ℃. 64㎕ of triethylamine was added thereto and, after 20 minutes, 40㎕ of methanesulfonyl chloride was added dropwise. After 20 minutes,

water was added and the reaction solution was extracted two times with dichloromethane. The extracts were combined, dried over $MgSO_4$ amd then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 69mg of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56-7.50(m, 2H), 7.32(d, 1H), 6.38(s, 1H), 4.61 (m, 1H), 3.79(bs, 1H), 3.70(s, 3H), 3.60-3.30(m, 2H), 2.98(s, 3H), 2.28(m, 2H), 2.30-1.70(m, 12H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

56mg of the compound obtained in the above a) was dissolved in 15mℓ of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for one day at room temperature and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vaccum pump. The dried product was then dissolved in 15mℓ of ethanol solution saturated with NH_3 gas. After 2 days, the resulting solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(3:1)] on NH-DM1020 silica to obtain 41mg of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.03(s, 1H), 7.35(m, 2H), 6.19(s, 1H), 4.55(m, 1H), 4.14(bs, 1H), 3.64(s, 3H), 3.43(m, 2H), 2.92(s, 3H), 2.67(m, 2H), 2.30-1.70(m, 12H)

Example 120 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 184)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

1.00g of the compound II-a obtained in Example 57-b) was dissolved in dichloromethane, and the resulting solution was cooled to 0 ℃. 0.75mℓ of triethylamine was added thereto and after 20 minutes, 0.42 mℓ of methanesulfonyl chloride was added dropwise. After 20 minutes, water was added and the reaction solution was extracted two times with dichloromethane. The extracts were combined, dried over $MgSO_4$ amd then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 524mg of the title compound as a white solid.

^1H NMR($CDCl_3$, ppm) : δ 7.48(m, 2H), 7.29(d, 1H), 6.37(s, 1H), 4.57(t, 1H), 4.20(bs, 1H), 4.10(m, 2H), 3.49-3.32(m, 2H), 2.99(s, 3H), 2.86-2.70(m, 2H), 2.30-1.65(m, 12H), 1.33(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

430mg of the compound obtained in the above a) was dissolved in 30mℓ of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for two days at room temperature and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vaccum pump. The dried product was then dissolved in 30mℓ of ethanol solution saturated with NH_3 gas. After 3 days, the resulting solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 184mg of the title compound as an orange solid.

^1H NMR($CDCl_3$, ppm) : δ 8.90(bs, 1H), 8.54(bs, 1H), 7.35(s, 1H), 6.15(s, 1H), 4.55(s, 1H), 4.16(m, 1H), 3.70(q, 2H), 2.95(s, 3H), 2.70(m, 2H), 2.30-1.70(m, 12H), 1.18(t, 3H)

Example 121 : Synthesis of ethyl 2-[(S)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 186)

a) Synthesis of tert-butyl (S)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

1.0g of the compound I-a obtained in Example 1-l) and 0.94g of 1-(tert-butoxycarbonyl)-L-proline were reacted according to the same procedure as Example 11-a) to obtain 736㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.51(m, 2H), 7.30(m, 1H), 6.38(d, 1H, J=9.95Hz), 4.35(m, 1H), 4.20-4.05(m, 2H), 3.85-3.35(m, 4H), 2.80(m, 2H), 2.30-1.70(m, 1H), 1.50-1.29(m, 11H)
IR(KBr) : 3400, 3000, 2220, 1700, 1660 cm^{-1}

b) Synthesis of 1-ethyl-2-[2-[(S)-1-((S)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

736㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 700㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58(s, 1H), 7.54(d, 1H, J=8.28Hz), 7.28(d, 1H, J=8.27Hz), 6.36(s, 1H), 4.50-4.10(m, 10H), 3.70-3.24(m, 4H), 2.80 (m, 2H), 2.50-1.71(m, 10H), 1.34(t, 3H)

c) Synthesis of ethyl 2-[(S)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

700㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-m) to obtain 746㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(t, 1H), 7.24(d, 1H), 6.50(s, 1H), 4.31(m, 1H), 4.17(m, 4H), 3.85(m, 1H), 3.48(m, 3H), 3.22(m, 1H), 2.82(m, 2H), 2.35-1.60(m, 10H), 1.43-1.20(m, 6H)

d) Synthesis of ethyl 2-[(S)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-

ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

746㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 233㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.77(s, 1H), 7.51(d, 1H, J=8.29Hz), 7.32(d, 1H, J=8.30Hz), 6.35(s, 1H), 4.30-4.12(m, 3H), 3.72(m, 1H), 3.58-3.10(m, 5H), 2.77(m, 2H), 2.60(m, 1H), 2.22-1.61(m, 10H), 1.27(t, 3H), 1.12(t, 3H)

ES-MS : 458(M+1)$^+$

IR(KBr) : 3200, 1630 cm^{-1}

Example 122 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoyl-methyl)-5-oxo-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 187)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-5-oxopyrrolidin-2-yl)carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

202㎎ of the compound 1-a obtained in Example 1-l) and 107㎎ of 5-oxopyrrolidine-(R)-2-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 136㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.52(m, 2H), 7.25(m, 1H), 6.50(s, 1H), 6.40 (s, 1H), 4.34-4.10(m, 4H), 3.58-3.46(m, 2H), 2.78(t, 2H, J=7.89 Hz), 2.44-1.66(m, 10H), 1.34(t, 3H, J=7.20Hz)

b) Synthesis of ethyl 2-[(R)-5-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-2-oxopyrrolidinyl]ethanoate:

160㎎ of the compound obtained in the above a) and 0.052㎖ of ethyl bromoacetate were dissolved in 3㎖ of anhydrous tetrahydrofuran, and 19㎎ of NaH was added thereto. The reaction mixture was heated

under refluxing for 5 hours with stirring. After 0.5㎖ of water was added dropwise, the reaction solution was evaporated under reduced pressure. The residue was diluted with 150㎖ of dichloromethane, washed with 30㎖ of water, dried over sodium sulfate and then filterd. The filtrate was then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(40:1)]. The fractions containing the desired product were combined and then evaporated to obtain 141㎎ of the title compound as a viscous oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.62-7.55(m, 2H), 7.32(m, 1H), 6.41(s, 1H), 4.69 (m, 2H), 4.29-4.11(m, 6H), 3.67-3.41(m, 2H), 2.79(t, 2H, J=7.98Hz), 2.56-1.65(m, 10H), 1.37(t, 3H, J=7.21Hz), 1.24(t, 3H, J=7.09Hz)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)-5-oxopyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

141㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 25㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.58-7.31(m, 2H), 6.40(s, 1H), 4.59(m, 1H), 4.21-4.14(m, 4H), 3.64-3.32(m, 3H), 2.82-2.73(m, 2H), 2.37-1.79(m, 10H), 1.30(t, 3H, J=7.15Hz)
ES-MS : 453(M+1)$^+$

Example 123 : Synthesis of 2-[(R)-5-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]-2-oxopyrrolidinyl]acetic acid (Compound 188)

12㎎ of 1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)-5-oxopyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine obtained in Example 122-c) was treated according to the same procedure as Example 44 to obtain 6㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.54-7.30(m, 2H), 6.38(s, 1H), 4.34(d, 1H, J=17.12Hz), 4.22-4.05(m, 3H), 3.63-3.34(m, 3H), 3.13 (d, 1H, J=17.17Hz), 2.81-2.70(m, 2H), 2.37-1.71(m, 10H), 1.29(t, 3H, J=7.15Hz)

ES-MS : 454(M+1)$^+$

Example 124 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(2-piperidyl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 189)

a) Synthesis of tert-butyl-2-[[(S)-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]piperilidine carboxylate:

1.7g of 1-ethyl-2-[[(S)-pyrrolidin-2-yl)ethyl]indole-6-carbonitrile was reacted with 1.75g of 1-(tert-butoxycarbonyl)-pipecolinic acid according to the same procedure as Example 11-a) to obtain 1.17g of the title compound as a pale yellow foam.

^{1}H NMR($CDCl_3$, ppm) : δ 7.63-7.53(m, 2H), 7.29-7.26(m, 1H), 6.37(s, 1H), 4.77(br, 1H), 4.31(br, 1H), 4.19-4.14(m, 2H), 3.93-3.89(m, 1H), 3.74-3.70(m, 1H), 3.52-3.48(m, 2H), 2.80-2.75(m, 2H), 2.19-2.14 (m, 1H), 2.01-1.62(m, 11H), 1.49-1.42(m, 9H), 1.35(t, 3H, J=7.20Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(2-piperidyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

40㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 19㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.77(s, 1H), 7.52-7.30(m, 2H), 6.33(s, 1H), 4.20-4.01(m, 3H), 3.56(m, 1H), 3.47-3.31(m, 2H), 3.02-2.50(m, 4H), 2.23-1.04(m, 12H), 1.26(m, 3H)

IR(KBr) : 3400, 2980, 1640, 1550, 1480 cm^{-1}
ES-MS : 396(M+1)$^+$

Example 125 : Synthesis of ethyl 2-[2-[[(S)-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]carbonyl]piperidinyl]ethanoate (Compound 190)

a) Synthesis of ethyl 2-[2-[[(S)-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidin-2-yl]carbonyl]piperidinyl]ethanoate:

120mg of tert-butyl-2-[[(S)-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]piperidine carboxylate obtained in Example 124-a) was treated according to the same procedure as Example 1-l) to obtain 86mg of the white solid product, which was then reacted with ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 85mg of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58(s, 1H), 7.56-7.27(m, 2H), 6.44(d, 1H, J=7.62Hz), 3.71(brs, 2H), 3.60-3.49(m, 2H), 3.40-3.28(m, 1H), 3.03-2.56(m, 4H), 2.36-1.65(m, 12H), 1.36(t, 3H, J=8.58Hz), 1.27-1.17(m, 3H)

b) Synthesis of ethyl 2-[2-[[(S)-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidin-2-yl]carbonyl]piperidinyl]ethanoate :

78mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 32mg of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.56-7.31(m, 2H), 6.36(s, 1H), 4.27-4.11(m, 3H), 4.02-3.83(m, 2H), 3.69-3.21(m, 5H), 3.94-2.50 (m, 4H), 2.22-1.46(m, 12H), 1.29(m, 3H), 1.14-1.05(m, 3H)
IR(KBr) : 3400, 2990, 1755, 1690, 1640, 1550, 1485 cm^{-1}
ES-MS : 482(M+1)$^+$

Example 126 : Synthesis of ethyl 2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidinyl]carbonyl]piperidinyl]acetate (Compound 191)

a) Synthesis of tert-butyl 2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-piperidinyl]carbonyl]piperidine carboxylate:

600㎎ of 1-ethyl-2-[2-((S)-piperidinyl)ethyl]indole-6-carbonitrile and 500㎎ of 1-[(tert-butoxy)carbonyl]piperidine-2-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 300 ㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.57(m, 2H), 7.30(m, 1H), 6.35(s, 1H), 4.95(br, 1H), 4.12(m, 2H), 3.90(br, 1H), 3.72(m, 1H), 2.71(m, 2H), 2.21(m, 1H), 1.84(m, 2H), 1.45(m, 9H), 1.33(m, 3H)

b) Synthesis of 1-ethyl-2-[2-[1-[((S)-2-piperidinyl)carbonyl]-2-piperidyl]ethyl]indole-6-carbonitrile:

280㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 210㎎ of the title compound as a pale yellow solid.

c) Synthesis of ethyl 2-[2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-piperidyl]carbonyl]piperidinyl]acetate:

200㎎ of the compound obtained in the above b) and 0.085㎖ of ethyl 2-bromoacetate were reacted according to the same procedure as Example 1-m) to obtain 120㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.38(s, 1H), 5.03(br, 1H), 4.11(m, 4H), 3.40(2H), 3.02(m, 2H), 2.75(m, 1H), 2.60(m, 2H), 2.20(m, 1H), 1.73(m, 3H), 1.32(m, 5H), 1.26(m, 3H), 1.17(m, 3H)

ES-MS : 479(M+1)$^+$, 501(M+Na)

d) Synthesis of ethyl 2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]piperidinyl]carbonyl]piperidinyl]acetate:

110㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 40㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(m, 1H), 7.56(m, 1H), 7.32(m, 1H), 6.34(s, 1H), 5.01(br, 1H), 4.12(m, 4H), 3.46(1H), 3.39(m, 2H), 3.02(m, 2H), 2.75(m, 1H), 2.59(m, 2H), 2.18(m, 1H), 1.76(m, 3H), 1.67(br, 6H), 1.32(m, 5H), 1.17(m, 3H)

IR(KBr) : 3400, 2900, 1610, 1460 cm^{-1}

ES-MS : 497(M+2), 519(M+Na)

Example 127 : Synthesis of methyl-2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetate (Compound 192)

a) Synthesis of methyl-2-[2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetate:

1g of tert-butyl-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]piperidine carboxylate obtained in Example 124-a) was treated according to the same procedure as Example 1-l) to obtain 1-ethyl-2-[2-[(S)-1-[(2-piperidinyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile, which was then reacted with methyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 631㎎ of the title compound as a pale yellow oil.

ES-MS : 450(M+1)

^{1}H NMR($CDCl_3$, ppm) : δ 7.58-7.53(m, 2H), 7.30-7.27(m, 1H), 6.46-6.43 (m, 1H), 4.35(br, 1H), 4.17-4.14(m, 2H), 3.67-3.64(m, 4H), 3.54-3.48(m, 2H), 3.40-3.32(m, 1H), 2.98(br, 1H), 2.79(br, 2H), 2.60-2.56(m, 1H), 2.24-2.21(m, 1H), 2.00-1.98(m, 4H), 1.74-1.64(m, 8H), 1.35(br, 3H)

b) Synthesis of methyl-2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetate:

630㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 200㎎ of the title compound as a pale yellow foam.

ES-MS : 468(M+1)$^+$

^{1}H NMR(MeOH-d_4, ppm) : δ 7.79(s, 1H), 7.57-7.51(m, 1H), 7.37-7.31(m, 1H), 6.37(s, 1H), 4.21-4.18(m, 3H), 3.62-3.58(m, 1H), 3.58-3.54 (m, 3H), 3.49-3.45(m, 2H), 3.29-3.23(m, 2H), 2.89-2.85(m, 1H), 2.76-2.72(m, 2H), 2.51-2.44(m, 1H), 2.18-2.05(m, 1H), 1.94-1.86 (m, 3H), 1.74-1.69(m, 4H), 1.55-1.50(m, 4H), 1.26-1.19(m, 3H)

Example 128 : Synthesis of 2-[2-[[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetic acid (Compound 193)

30㎎ of methyl-2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetate obtained in Example 127-b) was treated according to the same procedure as Example 44 to obtain 17 ㎎ of the title compound as a pale yellow solid.

ES-MS : 454(M+1)$^+$

^{1}H NMR(MeOH-d_4, ppm) : δ 7.80-7.78(m, 1H), 7.55-7.50(m, 1H), 7.35-7.31(m, 1H), 6.37(s, 1H), 4.22-4.18(m, 3H), 3.75-3.69(m, 1H), 3.61-3.50(m, 2H), 2.99-2.91(m, 3H), 2.78-2.75(m, 2H), 2.47-2.42 (m, 1H), 2.12-1.55(m, 12H), 1.25-1.19(m, 3H)

IR(KBr) : 3420, 2980, 1580 cm^{-1}

Example 129 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(3-piperidinyl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 194)

a) Synthesis of tert-butyl 3-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]

-pyrrolidinyl]carbonyl]piperidine carboxylate:

130㎎ of the compound I-a obtained in Example 1-l) and 1-[(tert-butoxy)carbonyl]piperidine-3-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 76㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60-7.29(m, 3H), 6.40(d, 1H, J=3.62Hz), 4.28-4.02(m, 5H), 3.71-3.42(m, 2H), 2.77(m, 4H), 2.53-1.59(m, 11H), 1.46(s, 9H), 1.38(t, 3H, J=7.10Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(3-piperidinyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

71㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 35㎎ of the title compound as a pale yellow solid.

^{1}H-NMR(MeOH-d_4, ppm) : δ 7.80(s, 1H), 7.54-7.31(m, 2H), 6.36(s, 1H), 4.22-4.02(m, 3H), 3.52(m, 2H), 2.92-2.28(m, 6H), 2.18-1.41(m, 11H)

IR(KBr) : 3380, 2990, 1630, 1540, 1480 cm^{-1}

ES-MS : 396(M+1)$^+$

Example 130 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(4-piperidinyl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 195)

a) Synthesis of tert-butyl 4-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]piperidine carboxylate:

148㎎ of the compound I-a obtained in Example 1-l) and 1-[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 63㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.58-7.24(m, 3H), 6.39(s, 1H), 4.30-3.95(m, 5H), 3.54(m, 2H), 2.89-2.68(m, 4H), 2.52-1.58(m, 11H), 1.46(s, 9H), 1.36(t, 3H, J=7.25Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

59㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 26㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.81-7.32(m, 3H), 6.37(s, 1H), 4.24-4.06(m, 4H), 3.53(m, 2H), 3.00-2.53(m, 7H), 2.18-1.50(m, 9H)
IR(KBr) : 3300, 2980, 1620, 1530, 1470 cm^{-1}
ES-MS : 396(M+1)$^+$

Example 131 : Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate (Compound 196)

a) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate:

109㎎ of 1-ethyl-2-[2-[(S)-1-(2-chloroacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile was treated according to the same procedure as Example 45-b) to obtain 133㎎ of the title compound as a viscous brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.54(m, 2H), 7.32(m, 1H), 6.41(s, 1H), 4.20-4.13(m, 5H), 3.61(dd, J=14.52Hz, 6.38Hz), 3.50(m, 2H), 3.33 (t, 1H, J=15.46Hz), 3.12(brs, 1H), 2.83-2.74(m, 2H), 2.38-1.70(m, 11H), 1.36(t, 3H, J=7.17Hz), 1.24(t, 3H, J=6.71Hz)

b) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]

-pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate:

130㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 35㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.78(s, 1H), 7.52-7.30(m, 2H), 6.36(s, 1H), 4.21-3.97(m, 5H), 3.56-3.27(m, 5H), 3.01(m, 1H), 2.83-2.74(m, 2H), 2.56-1.72(m, 11H), 1.29(t, 3H, J=7.12Hz), 1.08(t, 3H, J=7.04Hz)
IR(KBr) : 3350, 2980, 1730, 1620, 1520, 1460, 1160 cm^{-1}
ES-MS : 468(M+1)$^+$

Example 132 : Synthesis of 1-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylic acid (Compound 197)

22㎎ ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate was treated according to the same procedure as Example 44 to obtain 15㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.88-7.32(m, 3H), 6.42-6.33(m, 1H), 4.25-4.13(m, 3H), 3.50-3.08(m, 5H), 3.00-2.86(m, 1H), 2.76(m, 2H), 2.47-1.51(m, 11H), 1.28(t, 3H, J=7.20Hz)
IR(KBr) : 3350, 2960, 1700, 1650, 1450 cm^{-1}
ES-MS : 440(M+1)$^+$

Example 133 : Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylate (Compound 198)

a) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylate:

112㎎ of 1-ethyl-2-[2-[(S)-1-(2-chloroacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile was treated according to the same procedure as Example 45-b) to obtain 140㎎ of the title compound as a viscous brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.41(d, 1H, J=3.07Hz), 4.28-4.13(m, 5H), 3.73-3.30(m, 4H), 3.19(t, 1H), 3.03-2.95(m, 1H), 2.79(t, 2H, J=7.98Hz), 2.64-1.60(m, 13H), 1.36(t, 3H, J=7.22Hz), 1.29-1.23(m, 3H)

b) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylate:

136㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 43㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.77(s, 1H), 7.53-7.30(m, 2H), 6.35(s, 1H), 4.21-4.02(m, 5H), 3.59-3.03(m, 5H), 2.96-2.88(m, 1H), 2.79-2.69 (m, 2H), 2.45-1.37(m, 13H), 1.29(t, 3H, J=7.13Hz), 1.18-1.13(m, 3H)

IR(KBr) : 3300, 2960, 1730, 1620, 1520, 1460, 1180 cm^{-1}

ES-MS : 481.62(M+1)$^+$

Example 134 : Synthesis of 1-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylic acid (Compound 199)

27㎎ of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylate was treated according to the same procedure as Example 44 to obtain 14㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.71(s, 1H), 7.55-7.27(m, 2H), 6.29(s, 1H), 4.20-4.06(m, 3H), 3.61-3.35(m, 3H), 3.41(d, 1H, J=14.55Hz), 2.82

(d, 1H, J=14.65Hz), 2.93-2.64(m, 3H), 2.28-1.50(m, 13H), 1.27-1.19(m, 3H)

ES-MS : 454(M+1)$^+$

Example 135 : Synthesis of ethyl 2-[2-[2-[(S)-1-[(R)-1-acetyl-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]-acetate (Compound 222)

a) Synthesis of 2-(hydroxymethyl)indole-6-carbonitrile:

10g of ethyl 6-cyanoindole-2-carboxylate was treated according to the same procedure as Example 1-e) to obtain 6.8g of the title compound as a yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.63(s, 1H), 7.52(d, 1H), 7.15(m, 1H), 6.38(s, 1H), 4.67(s, 2H)

b) Synthesis of tert-butyl (S)-2-[2-(6-cyanoindol-2-yl)vinyl]pyrrolidine carboxylate:

1g of 2-(hydroxymethyl)indole-6-carbonitrile was treated according to the same procedure as Examples 1-f) and 1-m) to obtain 800㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.47(m, 2H), 7.24(m, 1H), 6.33(s, 1H), 4.40(m, 1H), 3.36(m, 2H), 2.15-1.70(m, 6H), 1.47(m, 9H)

c) Synthesis of tert-butyl (S)-2-[2-(6-cyanoindol-2-yl)ethyl]pyrrolidine carboxylate:

800㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-k) to obtain 620㎎ of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.66(s, 1H), 7.50(t, 1H), 7.20(m, 1H), 6.21(s,

1H), 3.92(m, 1H), 3.32(m, 2H), 2.80(m, 2H), 2.1-1.7(m, 6H), 1.6-1.35(m, 9H)

d) Synthesis of ethyl 2-[6-cyano-2-[2-[(S)-1-[(tert-butoxy)carbonyl]-pyrrolidin-2-yl]ethyl]indolyl]acetate:

620㎎ of the compound obtained in the above c) and 0.3㎖ of ethyl 2-bromoacetate were reacted with NaH in the presence of N,N-dimethyl-formamide to obtain 850㎎ of the title compound as a brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60(s, 1H), 7.51(s, 1H), 7.36(d, 1H), 6.46(s, 1H), 4.84(s, 2H), 4.32-4.20(m, 2H), 3.98(m, 1H), 3.43-3.27(m, 2H), 2.80-2.65(m, 2H), 1.95-1.67(m, 6H), 1.60-1.42(m, 9H), 1.37-1.23 (m, 3H)

e) Synthesis of ethyl 2-[6-cyano-2-[2-[(S)-1-[[(R)-1-[(tert-butoxy)-carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indolyl]acetate:

800㎎ of the compound obtained in the above d) was treated according to the same procedure as Examples 1-l) and 11-a) to obtain 340㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.63(s, 1H), 7.50(d, 1H), 7.20(d, 1H), 6.42(m, 1H), 4.68(s, 2H), 4.30-4.20(m, 1H), 4.10(m, 2H), 3.67-3.57(m, 1H), 3.51(m, 2H), 3.32(m, 2H), 2.10-1.60(m, 2H), 1.36-1.25(m, 9H), 1.10(m, 3H)

f) Synthesis of ethyl 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)car-bonyl]pyrrolidin-2-yl]ethyl]-6-cyanoindolyl]acetate:

300㎎ of the compound obtained in the above e) was treated according to the same procedure as Examples 1-l) and 1-m) to obtain 180㎎ of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.60(m, 1H), 7.50(s, 1H), 7.34(m, 1H), 6.47(s,

1H), 4.86(m, 2H), 4.35-4.17(m, 3H), 3.89(m, 1H), 3.70(m, 2H), 3.54(m, 2H), 2.30-1.90(m, 9H), 1.35(m, 6H)

g) Synthesis of ethyl 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate:

150㎎ of the compound obtained in the above f) was treated according to the same procedure as Example 1-n) to obtain 80㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.50(m, 2H), 6.32(s, 1H), 4.97(s, 2H), 4.65(m, 1H), 4.15(m, 3H), 3.86(m, 1H), 3.68(m, 2H), 3.39(m, 2H), 2.70(m, 2H), 2.19-1.82(m, 12H), 1.22(m, 3H)

ES-MS : 482(M+1)$^+$

Example 136 : Synthesis of 2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-1-(carbamoylmethyl)indole-6-carboxamidine (Compound 224)

30㎎ of ethyl 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)-carbonyl]pyrrolidin-2-yl]ethyl]-6-cyanoindolyl]acetate obtained in Example 135-g) was treated according to the same procedure as Example 1-n) to obtain 30㎎ of the title compound as a yellowish white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.74(s, 1H), 7.59(m, 1H), 7.36(m, 1H), 6.39(s, 1H), 4.87(s, 2H), 4.59(m, 1H), 4.29(m, 1H), 3.73(m, 3H), 2.75(m, 2H), 2.21(m, 2H), 2.09(s, 3H), 2.00-1.89(m, 9H)

ES-MS : 453(M+1)$^+$

Example 137 : Synthesis of 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetic acid (Compound 225)

40㎎ of ethyl 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)-carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate obtained in

Example 135 was treated according to the same procedure as Example 44 to obtain 15mg of the title compound as a white solid.

^{1}H NMR(MeOH-d_4+$CDCl_3$, ppm) : δ 7.46(m, 2H), 7.28(m, 1H), 6.37(s, 1H), 4.64(s, 2H), 4.53(s, 1H), 4.19(br, 1H), 3.79(m, 1H), 3.64(m, 3H), 2.75(m, 2H), 2.17(m, 3H), 2.03(s, 3H), 2.01-1.78(m, 7H), 1.28(m, 2H)

ES-MS : 451(M+1)$^+$

Example 138 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 242)

a) Synthesis of ethyl 5-bromoindole-2-carboxylate:

In a 500mℓ flask, 14g of 4-bromophenylhydrazine hydrochloride was dissolved in 170mℓ of ethanol, and 1.2mℓ of sulfuric acid and 8.5mℓ of ethyl pyruvate were added. The reaction mixture was stirred for about 2 hours at room temperature and evaporated under reduced pressure to dryness. To the residue was added 23mℓ of polyphosphoric acid, and the resulting solution was then stirred for 2 hours at 100℃-110℃. After water was added, the reaction solution was neutralized with saturated aqueous $NaHCO_3$ solution and then extratced two times with ethyl acetate. The extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(9:1)] to obtain 10g of the title compound as a brown solid.

^{1}H NMR($CDCl_3$, ppm) : δ 9.03(br, 1H), 7.82(s, 1H), 7.41(m, 1H), 7.31(m, 1H), 7.14(s, 1H), 4.40(q, 2H, J=7.1Hz), 1.41(t, 3H, J=7.1Hz)

b) Synthesis of ethyl 5-bromo-1-methylindole-2-carboxylate:

4.5g of the compound obtained in the above a) and 2.1mℓ of iodomethane were reacted according to the same procedure as Example

1-d) to obtain 5.9g of the title compound as a yellow oil.

c) Synthesis of ethyl 5-cyano-1-methylindole-2-carboxylate:

In a 500mℓ flask, 8.7g of the compound obtained in the above b) was dissolved in 430mℓ of 1-methylpyrrolidin-2-one, and 4.1g of CuCN was added thereto. The reaction mixture was stirred for 14 hours at 190℃-200℃, cooled to room temperature and then filtered. To the filtrate was added water, and the reaction solution was extracted two times with chloroform. The extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(3:1)] to obtain 6.5g of the title compound as a brown solid.

d) Synthesis of 1-methyl-2-(hydroxymethyl)indole-5-carbonitrile:

6g of the compound obtained in the above c) was treated according to the same procedure as Example 1-e) to obtain 2.4g of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.90(s, 1H), 7.42(m, 1H), 7.33(m, 1H), 6.53(s, 1H), 4.83(s, 2H), 3.84(s, 3H)
IR(KBr) : 3250, 2200, 1600, 1480 cm^{-1}

e) Synthesis of (5-cyano-1-methyl-2-indolyl)methyltriphenylphosphonium bromide:

2.4g of the compound obtained in the above d) was treated according to the same procedure as Example 1-f) to obtain 5.3g of the title compound as a pale pink solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.82(m, 3H), 7.62(m, 15H), 6.26(m, 1H), 5.19 (d, 2H), 3.08(s, 3H)

f) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-methylindol-2-yl)vinyl]-

pyrrolidine carboxylate:

5g of the compound obtained in the above e) was treated according to the same procedure as Example 1-j) to obtain 1.6g of the title compound as a yellow oil.

g) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-methylindol-2-yl)ethyl]-pyrrolidine carboxylate:

1.4g of the compound obtained in the above f) was treated according to the same procedure as Example 1-k) to obtain 1.3g of the title compound as a yellow oil.

h) Synthesis of 1-methyl-2-((S)-2-pyrrolidin-2-ylethyl)indole-5-carbonitrile:

1.2g of the compound obtained in the above g) was treated according to the same procedure as Example 1-l) to obtain 710mg of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.82(s, 1H), 7.35(m, 1H), 7.26(m, 1H), 6.32(s, 1H), 3.66(s, 3H), 3.19(m, 1H), 3.06(m, 2H), 2.97(m, 1H), 2.81(m, 2H), 1.94(m, 5H)

i) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(5-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

700mg of the compound obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 1g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.85(m, 1H), 7.36(m, 1H), 7.27(m, 1H), 6.34(s, 1H), 4.11(m, 1H), 3.80(m, 1H), 3.68(s, 3H), 3.61(m, 2H), 3.43(m, 3H), 2.82(m, 2H), 2.16-1.87(m, 9H), 1.42(s, 9H)

j) Synthesis of 1-methyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-5-carbonitrile:

1g of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 730㎎ of the title compound as a yellow oil.

k) Synthesis of methyl 2-[(R)-2-[[(S)-2-[2-(5-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

720㎎ of the compound obtained in the above j) and 0.35㎖ of ethyl 2-bromoacetate were reacted according to the same procedure as Example 1-m) to obtain 680㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.87(s, 1H), 7.44(m, 1H), 7.29(m, 1H), 6.40(s, 1H), 4.23(m, 1H), 4.12(m, 2H), 3.87(m, 1H), 3.72(s, 3H), 3.53(m, 2H), 3.22(m, 1H), 2.82(m, 3H), 2.01-1.89(m, 9H), 1.22(t, 3H, J=7.1Hz)

l) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

670㎎ of the compound obtained in the above k) was treated according to the same procedure as Example 1-n) to obtain 200g of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.98(s, 1H), 7.49(m, 1H), 7.30(m, 1H), 6.56(s, 1H), 4.70-4.39(br, 2H), 4.28(m, 1H), 4.12(q, 2H), 3.81(m, 1H), 3.66(s, 3H), 3.60(m, 2H), 3.29(m, 1H), 2.77(m, 3H), 2.35(m, 1H), 2.17(m, 1H), 2.00-1.78(m, 9H), 1.24(t, 3H)

IR(KBr) : 3300, 2900, 1720, 1620 cm^{-1}

ES-MS : 454(M+1)$^+$, 476(M+Na)

Example 139 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[(S)-2-(5-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-

acetate (Compound 243)

a) Synthesis of ethyl 5-bromo-1-ethylindole-2-carboxylate:

4.5g of ethyl 5-bromoindole-2-carboxylate and 2.7㎖ of iodoethane were reacted according to the same procedure as Example 1-d) to obtain 5.2g of the title compound as a yellow oil.

b) Synthesis of ethyl 5-cyano-1-ethylindole-2-carboxylate:

In a 500㎖ flask, 7.7g of the compound obtained in the above a) was dissolved in 360㎖ of 1-methylpyrrolidin-2-one, and 3.5g of CuCN was added thereto. The reaction mixture was stirred for 14 hours at 190℃-200℃, cooled to room temperature and then filtered. To the filtrate was added water, and the reaction solution was extracted two times with chloroform. The extracts were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(3:1)] to obtain 5.4g of the title compound as a brown solid.

c) Synthesis of 1-ethyl-2-(hydroxymethyl)indole-5-carbonitrile:

5g of the compound obtained in the above b) was treated according to the same procedure as Example 1-e) to obtain 2.9g of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.91(s, 1H), 7.44(m, 1H), 7.38(m, 1H), 6.52(s, 1H), 4.83(s, 2H), 4.32(q, 2H, J=7.2Hz), 1.42(t, 3H, J=7.2Hz)
IR(KBr) : 3450, 2200, 1600, 1480 cm^{-1}

d) Synthesis of (5-cyano-1-ethyl-2-indolyl)methyltriphenylphosphonium bromide:

2.8g of the compound obtained in the above c) was treated according to the same procedure as Example 1-f) to obtain 6g of the title

compound as a pale pink solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.92(m, 3H), 7.74(m, 15H), 6.29(m, 1H), 3.78 (q, 2H, J=7.1Hz), 3.33(m, 2H), 1.12(t, 3H, J=7.1Hz)

e) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-ethylindol-2-yl)vinyl]-pyrrolidine carboxylate:

5g of the compound obtained in the above d) was treated according to the same procedure as Example 1-j) to obtain 1.7g of the title compound as a yellow oil.

f) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidine carboxylate:

1.6g of the compound obtained in the above e) was treated according to the same procedure as Example 1-k) to obtain 1.5g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.85(s, 1H), 7.38(m, 1H), 7.26(m, 1H), 6.35(s, 1H), 4.14(q, 2H, J=7.2Hz), 3.95(br, 1H), 3.37(m, 2H), 2.75(m, 2H), 1.92-1.76(m, 6H), 1.47(s, 9H), 1.35(t, 3H, J=7.2Hz)

g) Synthesis of 1-ethyl-2-((S)-2-pyrrolidin-2-ylethyl)indole-5-carbonitrile:

1.4g of the compound obtained in the above f) was treated according to the same procedure as Example 1-l) to obtain 940㎎ of the title compound as a yellow oil.

h) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(5-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

930㎎ of the compound obtained in the above g) was treated according to the same procedure as Example 11-a) to obtain 960㎎ of the

title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.85(m, 1H), 7.35(m, 1H), 7.28(m, 1H), 6.36(s, 1H), 4.15(m, 3H), 3.80(m, 1H), 3.62(m, 2H), 3.43(m, 3H), 2.79(m, 2H), 2.11-1.85(m, 9H), 1.42(s, 9H)

i) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-5-carbonitrile:

960㎎ of the compound obtained in the above h) was treated according to the same procedure as Example 1-l) to obtain 650㎎ of the title compound as a yellow oil.

j) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

640㎎ of the compound obtained in the above i) and 0.3㎖ of ethyl 2-bromoacetate were reacted according to the same procedure as Example 1-m) to obtain 650㎎ of the title compound as a pale yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(s, 1H), 7.38(m, 1H), 7.28(m, 1H), 6.40(s, 1H), 4.27(m, 1H), 4.13(m, 4H), 3.87(m, 1H), 3.56(m, 2H), 3.22(m, 1H), 2.78(m, 3H), 2.02-1.86(m, 9H), 1.35(t, 3H, J=7.1Hz), 1.22(t, 3H, J=7.1Hz)

k) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

630㎎ of the compound obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 150㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.15(s, 1H), 7.55(m, 1H), 7.30(m, 1H), 6.71(s, 1H), 6.10-5.80(br, 2H), 4.38(m, 1H), 4.11(m, 4H), 3.73(m, 1H), 3.44(m, 2H), 3.38(m, 1H), 2.72(m, 3H), 2.45(m, 1H), 2.20(m, 1H),

1.99-1.70(m, 9H), 1.26(m, 6H)
IR(KBr) : 3200, 3000, 1740, 1620 cm^{-1}
ES-MS : 468(M+1)$^+$

Example 140 : Synthesis of 6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yllethyl]naphthalene-2-carboxamidine (Compound 244)

1g of 7-cyanonaphthalene-3-methyltriphenylphosphonium bromide and 390mg of (S)-1-(t-butoxycarbonyl)-2-pyrrolidinal were dissolved in a mixed solvent of 15mℓ of tetrahydrofuran and 15mℓ of ethanol, and 360$\mu\ell$ of DBU (1,8-diazabicyclo[5.4.0]undec-7ene) was added at room temperature. The reaction solution was stirred overnight at room temperature and distilled under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(3:1)]. The fractions containing the desired product were combined and distilled under reduced prssure to obtain the product, tert-butyl (S)-2-[2-(6-cyano-2-naphthyl)vinyl]pyrrolidine carboxylate. 410mg of this product thus obtained was dissolved in 15mℓ of ethanol and then hydrogenated in the presence of 50mg of Pd/C(10% w/w) for 2 hours under normal pressure with stirring. The reaction solution was filtered under reduced pressure to remove Pd/C, and the filtrate was distilled under reduced pressure and dried under reduced pressure. The residue was dissolved in 10mℓ of dichloromethane, and 3mℓ of trifluoroacetic acid was added. The mixture thereby obtaned was stirred overnight at room temperature, and excess of dichloromethane was added thereto. The organic layer was separated, washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and then filtered under reduced pressure. The filtrate was distilled under reduced pressure to obtain 320mg of the oily product, 6-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile. 85mg of the resulting oily product was then treated according to the same procedure as Example 1-m) to obtain 50mg of the compound 6-[2-[(S)- 1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbonitrile, which was then treated according to the same procedure as Example 1-n) to obtain 30mg of the title compound as a yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.20(d, 1H), 7.83(m, 2H), 7.68(m, 2H), 7.37 (d, 1H), 7.21-7.12(m, 5H), 6.98(d, 1H), 6.76(d, 1H), 4.05(m, 1H), 3.59(m, 2H), 3.37(m, 4H), 2.70(t, 2H), 2.15(m, 1H), 1.93-1.79(m, 7H), 1.70(m, 1H)

Example 141 : Synthesis of methyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 245)

a) Synthesis of methyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-2-naphthyl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

250㎎ of 6-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile was treated according to the same procedure as Example 11-a) to obtain 256㎎ of tert-butyl (R)-2-[[(S)-2-[2-(6-cyano-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate. 150㎎ of the compound thereby obtained was reacted according to the same procedure as Example 1-l) to obtain 134㎎ of 6-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]-ethyl]naphthalene-2-carbonitrile. Thereafter, 130㎎ of the compound thus obtained was treated according to the same procedure as Example 1-m) to obtain 129㎎ of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.17(s, 1H), 7.92- 7.79(m, 2H), 7.73(s, 1H), 7.50 (m, 2H), 4.19(bs, 1H)

b) Synthesis of methyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-2-naphthyl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

124㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 48㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.35(s, 1H), 7.95(m, 2H), 7.89(m, 2H), 7.54(d, 1H, J=11.73Hz), 4.20-4.00(m, 3H), 3.79(m, 1H), 3.62(m, 2H), 3.46 (d, 2H, J=19.11Hz), 3.20(m, 1H), 3.00(m, 1H), 2.98-2.70(m, 3H),

2.33-1.70(m, 11H)
ES-MS : 451(M+1)$^+$

Example 142 : Synthesis of 7-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamidine (Compound 246)

a) Synthesis of tert-butyl (S)-2-(2-(7-cyano-2-naphthyl)vinyl)pyrrolidine carboxylate:

5.6g of 7-cyanonaphthalene-2-methyltriphenylphosphonium bromide was reacted according to the same procedure as Example 1-j) to obtain 2.9g of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 8.24-7.54(m, 6H), 6.55(bs, 1H), 6.30(bs, 1H), 4.51(bd, 1H), 3.49(s, 2H), 2.17-1.82(m, 4H), 1.83-1.26(m, 9H)

b) Synthesis of 7-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile:

2.9g of the compound obtained in the above a) was treated according to the same procedure as Example 1-k) to obtain 2.7g of the product, which was then treated according to the same procedure as Example 1-l) to obtain 1.6g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.79(s, 1H), 7.76(d, 1H, J=8.46Hz), 7.68(d, 1H, J=8.42Hz), 7.54-7.48(t, 2H), 7.37(d, 1H, J=8.43Hz), 3.49(t, 1H), 3.26(m, 2H), 2.91-2.82(m, 2H), 2.30-1.68(m, 6H)
ES-MS : 251(M+1)$^+$

c) Synthesis of 7-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbonitrile:

445㎎ of the compound obtained in the above b) and 0.47㎖ of phenyl acetylchloride were reacted according to the same procedure as Example 1-m) to obtain 298㎎ of the title compound.

^{1}H NMR($CDCl_3$, ppm) : δ 8.14(s, 1H), 7.86-7.78(q, 2H), 7.67(s, 1H), 7.55-7.51(m, 2H), 7.32-6.92(m, 5H), 4.21(m, 1H), 3.64(s, 1H), 3.46(m, 2H), 2.80(t, 2H, J=8.16Hz), 2.33(m, 1H), 2.04-1.59(m, 5H)

d) Synthesis of 7-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamidine:

270㎎ of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 128㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.08(s, 1H), 7.77-7.61(m, 4H), 7.34-7.32(d, 1H, J=8.38Hz), 7.20-7.13(m, 3H), 6.94(m, 1H), 6.73(d, 1H), 4.08 (bs, 1H), 3.56(s, 2H), 3.45-3.30(m, 2H), 2.67(t, 2H), 2.20-1.50(m, 6H)

ES-MS : 386(M+1)$^+$

Example 143 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(7-amidino-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 247)

a) Synthesis of 7-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbonitrile:

450㎎ of 7-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile obtained in Example 142-b) was treated according to the same procedure as Example 11-a) to obtain 643㎎ of tert-butyl (R)-2-[[(S)-2-[2-(7-cyano-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate, which was then treated according to the same procedure as Example 1-l) to obtain 472㎎ of the title compound as a brown oil.

^{1}H NMR($CDCl_3$, ppm) : δ 8.17(s, 1H), 7.90(d, 1H, J=8.83Hz), 7.79(d, 1H, J=8.49Hz), 7.73(s, 1H), 7.49(d, 2H), 4.35(t, 1H), 4.02(m, 1H), 3.52(m, 1H), 3.32(m, 2H), 2.76(m, 2H), 2.36(m, 1H), 2.23(m, 1H), 2.10-1.80(m, 8H), 1.74-1.60(m, 1H)

ES-MS : 348(M+1)$^+$

b) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(7-cyano-2-naphthyl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

572㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-m) to obtain 700㎎ of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.18(s, 1H), 7.90-7.70(m, 3H), 7.50(m, 2H), 4.01(m, 2H), 3.89(m, 1H), 3.67(m, 1H), 3.54-3.12(m, 5H), 3.05(m, 1H), 2.92(m, 1H), 2.73(m, 2H), 2.20-1.50(m, 10H), 1.06(t, 3H)
ES-MS : 434(M+1)$^+$, 456(M+Na)

c) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(7-amidino-2-naphthyl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

650㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 148㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.08(s, 1H), 7.78-7.76(m, 4H), 7.34(m,1H), 4.00(m, 2H), 3.90(m, 1H), 3.65(m, 1H), 3.57-3.15(m, 4H), 3.07(m, 1H), 2.88(m, 1H), 2.65(m, 2H), 2.17-1.50(m, 10H), 1.07(t, 3H)
ES-MS : 451(M+1)$^+$, 474(M+Na)
IR(KBr) : 3200, 1220 cm^{-1}

Example 144 : Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo[b]furan-5-carboxamidine (Compound 248)

a) Synthesis of ethyl 2-(4-bromo-2-formylphenoxy)acetate:

In a 1 ℓ flask, 30g of 5-bromosalicyl aldehyde was stirred in 500 ㎖ of acetone solvent at room temperature, and then 26.8g of K_2CO_3 was slowly added thereto. After the mixture thereby obtained was stirred for

30 minutes, 21.5㎖ of ethyl bromoacetate was slowly added dropwise thereto and the reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, the reaction solution was evaporated. To the residue was added dichloromethane and the resulting precipitate was filtered and washed two times with water. The organic layers were combined, dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 43g of the title compound as a yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 10.45(s, 1H), 7.95(d, 1H, J=2.59Hz), 7.60(dd, 1H, J=8.79Hz, 2.61Hz), 6.75(d, 1H, J=8.62Hz), 4.75(s, 2H), 4.20(q, 2H, J=7.14Hz), 1.25(t, 3H, J=7.15Hz)

ES-MS : 288(M+1)$^+$

b) Synthesis of ethyl 5-bromobenzo[d]furan-2-carboxylate:

In a 1 ℓ flask, 2.96g of Na was slowly added to 250㎖ of ethanol solvent, and this mixture was stirred for 30 minutes. 42g of the compound obtained in the above a) was slowly added dropwise thereto at room temperature. The reaction solution was stirred for 2 hours and then evaporated under reduced pressure. The residue was extracted two times with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and then evaporated to obtain 11.7g of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 4.40(q, 2H, J=7.13Hz), 1.40(t, 3H, J=7.13Hz)

ES-MS : 270(M+1)$^+$

c) Synthesis of ethyl 5-cyanobenzo[d]furan-2-carboxylate:

In a 250㎖ flask, 24.7g of the compound obtained in the above b) was dissolved in 100㎖ of N-methylpyrrolidinone, and 16.53g of CuCN

and 1.48g of $CuSO_4$ catalyst were added thereto. The reaction mixture was refluxed for one hour at 200-220℃ with stirring. The reaction solution was then stirred for 30 minutes at room temperature. After excessive amount of water was added, the reaction solution was stirred and then filtered. The residue was washed three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:5)]. The fractions containing the desired product were combined and then evaporated to obtain 6.39g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.05(s, 1H), 7.70(m, 2H), 7.55(s, 1H), 4.45(q, 2H, J=7.10Hz), 1.45(t, 3H, J=7.12Hz)
ES-MS : 216(M+1)$^+$

d) Synthesis of 2-(hydroxymethyl)benzo[b]furan-5-carbonitrile:

6.39g of the compound obtained in the above c) was treated according to the same procedure as Example 1-e) to obtain a stoichiometric amount of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.0(s, 1H), 7.60(s, 2H), 6.75(s, 1H), 4.80(s, 1H), 4.65(s, 1H)
ES-MS : 174(M+1)$^+$

e) Synthesis of benzo[b]furan-5-carbonitrile-2-methyltriphenylphosphonium bromide:

5.34g of the compound obtained in the above d) was treated according to the same procedure as Example 1-f) to obtain 14.8g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.95-7.60(m, 16H), 7.45(m, 1H), 7.25(m, 2H), 6.05(d, 2H)

f) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)vinyl]-pyrrolidine carboxylate:

11.8g of the compound obtained in the above e) was treated according to the same procedure as Example 1-j) to obtain 3.99g of the title compound as a fluorescent yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 6.55(s, 1H), 6.50-6.10 (m, 2H), 4.45(m, 1H), 3.45(br, 2H), 2.0-1.70(m, 4H), 1.40(br, 9H)
ES-MS : 339(M+1)$^+$

g) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)ethyl]-pyrrolidine carboxylate:

2.09g of the compound obtained in the above f) was treated according to the same procedure as Example 1-k) to obtain 1.75g of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 6.50(s, 1H), 3.90(m, 1H), 3.40(m, 2H), 2.80(m, 2H), 2.30-1.60(m, 6H), 1.40(br, 9H)

h) Synthesis of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-5-carbonitrile:

1.55g of the compound obtained in the above g) was treated according to the same procedure as Example 1-l) to obtain a stoichiometric amount of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 9.30(br, 1H), 7.75(s, 1H), 7.40(m, 2H), 3.50(m, 1H), 3.25(m, 2H), 2.90(m, 2H), 2.35-1.80(m, 4H), 1.70(m, 1H)
ES-MS : 241(M+1)$^+$

i) Synthesis of 1-((S)-2-(2-(5-ethynylbenzo[d]furan-2-yl)ethyl)pyrrolidinyl)-2-phenylethan-1-one:

220mg of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-5-carbonitrile obtained in the above h) and 180mg of phenylacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 200mg of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(s, 2H), 7.45(m, 2H), 7.25(m, 5H), 6.55(s, 1H), 4.25(m, 1H), 3.65(m, 2H), 3.45(m, 2H), 2.80(m, 2H), 2.30(m, 1H), 2.10-1.80(m, 3H), 1.70(m, 2H)

ES-MS : 358(M+1)$^+$

j) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo-[b]furan-5-carboxamidine:

190mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-n) to obtain 180mg of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.70(s, 1H), 7.55-7.10(m, 7H), 6.50(s, 1H), 4.25 (m, 1H), 3.65(s, 2H), 3.45(m, 1H), 2.80(t, 2H, J=7.80Hz), 2.30(m, 1H), 2.10-1.80(m, 3H), 1.70(m, 2H)

ES-MS : 376(M+1)$^+$

IR(KBr) : 3300, 2950, 2800, 1650 cm^{-1}

Example 145 : Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]vinyl]benzo[b]furan-5-carboxamidine (Compound 249)

a) Synthesis of 2-(2-pyrrolidin-(S)-ylvinyl)benzo[b]furan-5-carbonitrile:

490mg of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)vinyl]-pyrrolidine carboxylate obtained in Example 144-f) was treated according to the same procedure as Example 1-l) to obtain a stoichiometric amount of the title compound as a colorless solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(m, 1H), 7.45(m, 2H), 6.65-6.30(m, 3H), 4.10(m, 1H), 3.35-3.15(m, 2H), 2.40-1.75(m, 4H)

ES-MS : 239(M+1)$^+$

b) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]vinyl]benzo-[b]furan-5-carbonitrile:

450㎎ of the compound obtained in the above a) and 0.3㎖ of phenylacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 344㎎ of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(m, 1H), 7.45(m, 2H), 7.40-7.15(m, 5H), 6.65-6.20(m, 3H), 4.75(m, 1H), 3.80-3.40(m, 4H), 2.25-1.75(m, 4H)

ES-MS : 357(M+1)$^+$

c) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]vinyl]benzo-[b]furan-5-carboxamidine:

223㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 190㎎ of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(m, 2H), 7.60-7.0(m, 7H), 6.70-6.20(m, 3H), 5.20-4.80(br, 3H), 3.75-3.40(m, 4H), 2.25-1.75(m, 4H)

ES-MS : 374(M+1)$^+$

IR(KBr) : 3200, 2950, 2850, 1650 cm^{-1}

Example 146 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-amidino-benzo[d]furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 250)

a) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(5-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

447㎎ of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-5-carbonitrile

obtained in Example 144-h was treated according to the same procedure as Example 11-a) to obtain 370㎎ of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(m, 1H), 7.40(m, 2H), 6.55(d, 1H), 4.40(m, 1H), 4.20(m, 1H), 3.85-3.30(m, 4H), 2.85(m, 2H), 2.45-1.60(m, 10H), 1.40(br, 9H)

ES-MS : 438(M+1)$^+$

b) Synthesis of 2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]-ethyl]benzo[b]furan-5-carbonitrile:

240㎎ of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 200㎎ of the title compound as a pale yellow foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(s, 1H), 7.40(m, 2H), 6.55(s, 1H), 4.55(m, 1H), 4.15(m, 1H), 3.60(m, 1H), 3.40(m, 3H), 2.75(m, 2H), 2.45(m, 1H), 2.25(m, 1H), 2.15-1.70(m, 8H)

c) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

203㎎ of the compound obtained in the above b) was treated according to the same procedure as Example 1-m) to obtain 248㎎ of the title compound as a pale yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 6.65(s, 1H), 4.30-4.0 (m, 3H), 3.85(m, 1H), 3.65-3.35(m, 4H), 3.20(m, 1H), 2.80(m, 3H), 2.30(m, 1H), 2.15(m, 1H), 2.10-1.60(m, 8H), 1.25(t, 3H, J=7.14Hz)

ES-MS : 424(M+1)$^+$

d) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(5-amidinobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate :

200㎎ of the compound obtained in the above c) was treated

according to the same procedure as Example 1-n) to obtain 100㎎ of the title compound as a pale yellowish white foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.90(s, 1H), 7.50(m, 2H), 6.65(s, 1H), 4.45(m, 1H), 4.20-3.95(m, 4H), 3.65(m, 1H), 3.50(m, 1H), 3.35(m, 1H), 3.15(m, 1H), 2.80(m, 1H), 2.45(m, 1H), 2.25(m, 1H), 2.10-1.70(m, 9H), 1.15(t, 3H, J=7.10Hz)

ES-MS : 441$(M+1)^+$

IR(KBr) : 3200, 2950, 1750, 1670 cm^{-1}

Example 147 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidinobenzo[d]furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 251) and 2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]benzo[b]furan-6-carboxamidine

a) Synthesis of 3-bromo-1-(2-bromoprop-2-enyloxy)benzene:

In a 1ℓ flask, 25g of 5-bromophenol was stirred in 250㎖ of dimethylformamide at room temperature, and 39.9g of K_2CO_3 was slowly added thereto. After the mixture thereby obtained was stirred for 30 minutes, 22.4㎖ of 2,3-dibromopropene was slowly added dropwise thereto and the reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, excessive amount of water was added to the reaction solution, which was then extracted three times with ether. The combined organic layer was dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: hexane]. The fractions containing the desired product were combined and then evaporated to obtain 37.1g of the title compound as a yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.10(m, 3H), 6.82(m, 1H). 5.96(s, 1H), 5.68(s, 1H), 4.60(s, 2H)

b) Synthesis of 5-bromo-2-(2-bromoprop-2-enyl)phenol:

In a 500mℓ flask, 240mℓ of 1N-BBr_3 was slowly added over one hour to 37g of the compound obtained in the above a) in 250mℓ of CS_2 solvent, and this mixture was then stirred for 6 hours. The reaction was quenched with 5N HCl at 0℃. The reaction solution was evaporated under reduced pressure and extracted two times with ether. The combined organic layer was dried over $MgSO_4$ and then evaporated to obtain 24.0g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.10-6.90(m, 3H), 5.55(d, 1H, J=1.40Hz), 5.50(d, 1H, J=1.60Hz), 5.05(s, 1H), 3.70(s, 2H)

c) Synthesis of 6-bromo-2-methylbenzo[b]furan:

In a 250mℓ flask, 24.0g of the compound obtained in the above b) was dissolved in 50mℓ of ethanol at room temperature, and 200mℓ of 2M NaOEt was slowly added dropwise thereto. The reaction solution was refluxed for 5 hours with stirring and then evaporated under reduced pressure. The residue was extracted three times with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:30)]. The fractions containing the desired product were combined and then evaporated to obtain 11.3g of the title compound as a pale yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(s, 1H), 7.30(s, 2H), 6.30(s, 1H), 2.40(s, 3H)

d) Synthesis of 2-methylbenzo[b]furan-6-carbonitrile:

11.3g of the compound obtained in the above c) was treated according to the same procedure as Example 144-c) to obtain 381mg of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.69(s, 1H), 7.50(ddd, 2H, J=24.96Hz, 8.02Hz, 1.04Hz), 6.45(s, 1H), 2.50(s, 2H)

e) Synthesis of 2-(bromomethyl)benzo[b]furan-6-carbonitrile:

380㎎ of the compond obtained in the above d) was dissolved in 100㎖ of carbon tetrachloride, and 472㎎ of NBS (N-bromosuccinimide) was added thereto. The reaction solution was refluxed for 6 hours with stirring and then evaporated under reduced pressure. The residue was then extracted three times with ethyl acetate. The combined oragnic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/ n-hexane(1:7)]. The fractions containing the desired product were combined and then evaporated to obtain 520㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(s, 1H), 7.55(m, 2H), 6.80(s, 1H), 4.60(s, 2H)

f) Synthesis of benzo[b]furan-6-carbonitrile-2-methyl-triphenylphosphonium bromide:

520㎎ of the compound obtained in the above e) was treated according to the same procedure as Example 1-f) to obtain 770㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.90-7.35(m, 19H), 6.10(d, 2H)

g) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)vinyl]-pyrrolidine carboxylate:

770㎎ of the compound obtained in the above f) was treated according to the same procedure as Example 1-j) to obtain 308㎎ of the title compound as a fluorescent yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.70(m, 1H), 7.50(m, 2H), 6.70-6.20(m, 3H), 4.50 (m, 1H), 3.45(br, 2H), 2.25-1.70(m, 4H), 1.40(br, 9H)

h) Synthesis of 2-((2S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-6-carboni-

trile:

308㎎ of the compound obtained in the above g) was treated according to the same procedure as Example 1-k) to obtain 270㎎ of the yellow liquid product, which was then treated according to the same procedure as Example 1-l) to obtain 229㎎ of the title compound as a yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.61(s, 1H), 7.45(dd, 2H, J=23.51Hz, 8.02Hz), 6.50(s, 1H), 3.50(m, 1H), 3.30(m, 2H), 2.92(m, 2H), 2.49-1.88(m, 5H), 1.71(m, 1H)

ES-MS : 241(M+1)$^+$

i) Synthesis of tert-butyl (R)-2-[[(S)-2-[2-(6-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

228㎎ of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-6-carbonitrile obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 167㎎ of the title compound as a yellowish white foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.80(m, 1H), 7.40(m, 2H), 6.55(d, 1H), 4.40(m, 1H), 4.20(m, 1H), 3.85-3.30(m, 4H), 2.85(m, 2H), 2.45-1.60(m, 10H), 1.40(br, 9H)

j) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

167㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 100㎎ of the white foamy product, which was then reacted with ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 60㎎ of the title compound as a white foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(s, 1H), 7.55(m, 2H), 6.80(s, 1H), 4.30-4.0

(m, 3H), 3.85(m, 1H), 3.50(m, 2H), 3.20(m, 1H), 2.80(m, 3H), 2.40-1.60(m, 12H), 1.25(t, 3H, J=7.14Hz)

k) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidinobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate :

60㎎ of the compound obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 4.2㎎ of the title compound as a white foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65(s, 1H), 7.45(m, 2H), 6.60(s, 1H), 5.05(br, 3H), 4.30-4.0(m, 3H), 3.85(m, 1H), 3.50(m, 4H), 3.20(m, 1H), 2.80 (m, 3H), 2.40-1.60(m, 10H), 1.47(t, 3H, J=7.14Hz)

ES-MS : 442(M+2)$^+$

l) Synthesis of 2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]-carbonyl]pyrrolidin-2-yl]ethyl]benzo[b]furan-6-carboxamidine:

60㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 3.2㎎ of the title compound as a yellow foamy solid.

^{1}H NMR(CD_3OD, ppm) : δ 7.75(s, 1H), 7.50(m, 2H), 6.55(s, 1H), 4.05(m, 1H), 3.60-3.25(m, 3H), 3.10(m, 1H), 3.0-2.60(m, 3H), 2.40(m, 1H), 2.15(m, 1H), 2.15-1.55(m, 10H)

ES-MS : 413(M+2)$^+$

Example 148 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-3-methylbenzo[d]furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-acetate (Compound 252)

a) Synthesis of 1-(4-bromo-2-hydroxyphenyl)ethan-1-one:

In a 1 ℓ flask, 25g of 5-bromoanisole was stirred in 250㎖ of CS_2

solvent at 0℃, and 12.4mℓ of acetyl chloride was added and 53.5g of $AlCl_3$ was slowly added portionwise thereto. After the addition was completed, the reaction solution was refluxed for one hour with stirring. The reaction was quenched with 2N HCl. Excessive amount of water was added and the reaction solution was extracted three times with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:10)]. The fractions containing the desired product were combined and then evaporated to obtain 7.68g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 12.3(s, 1H), 7.57(d, 1H, J=8.56Hz), 7.17(d, 1H, J=1.92Hz), 7.04(dd, 1H, J=8.49Hz, 1.98Hz)
ES-MS : 237(M+1)$^+$

b) Synthesis of ethyl 2-(5-bromo-2-acetylphenoxy)acetate:

7.68g of the compound obtained in the above a) was treated in acetone solvent according to the same procedure as Example 42 to obtain 3.58g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65(d, 1H, J=8.34Hz), 7.20(dd, 1H, J=8.32Hz, 1.76Hz), 6.95(d, 1H, J=1.64Hz), 4.70(s, 2H), 4.25(q, 2H, J=7.15 Hz), 2.65(s, 3H), 1.35(t, 3H, J=7.11Hz)

c) Synthesis of ethyl 6-bromo-3-methylbenzo[d]furan-2-carboxylate:

3.58g of the compound obtained in the above b) was treated according to the same procedure as Example 144-b) to obtain 1.26g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.70(s, 1H), 7.40(m, 2H), 4.40(q, 2H, J=7.13Hz), 2.50(s, 3H), 1.40(t, 3H, J=7.13Hz)
ES-MS : 283(M+1)$^+$

d) Synthesis of ethyl 6-cyano-3-methylbenzo[d]furan-2-carboxylate:

7.52g of the compound obtained in the above c) was treated according to the same procedure as Example 144-c) to obtain 790mg of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.85(s, 1H), 7.70(d, 1H, J=8.24Hz), 7.55(dd, 1H, J=8.15Hz, 1.26Hz), 4.45(q, 2H, J=7.14Hz), 2.60(s, 3H), 1.45(t, 3H, J=7.12Hz)

ES-MS : 230$(M+1)^+$

e) Synthesis of 2-(hydroxymethyl)-3-methylbenzo[b]furan-6-carbonitrile:

789mg of the compound obtained in the above d) was treated according to the same procedure as Example 1-e) to obtain 459mg of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.75(s, 1H), 7.55(d, 1H, J=7.96Hz), 7.40(d, 1H, J=8.03Hz), 4.60(s, 2H), 2.15(s, 3H)

f) Synthesis of benzo[b]furan-6-carbonitrile-2-methyl-triphenylphosphonium bromide:

459mg of the compound obtained in the above e) was treated according to the same procedure as Example 1-f) to obtain 855mg of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.95-7.35(m, 18H), 5.85(d, 2H), 2.25(s, 3H)

g) Synthesis of tert-butyl (S)-2-[2-(6-cyano-3-methylbenzo[d]furan-2-yl)vinyl]pyrrolidine carboxylate:

850mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-j) to obtain 344mg of the title compound as a fluorescent yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65(s, 1H), 7.45(m, 2H), 6.40(br, 2H), 4.50(m, 1H), 3.45(br, 2H), 2.25(s, 3H), 2.05-1.70(m, 4H), 1.40(br, 9H)

h) Synthesis of 3-methyl-2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-6-carbonitrile:

344㎎ of the compound obtained in the above g) was treated according to the same procedure as Example 1-k) to obtain 340㎎ of the colorless liquid product, which was then treated according to the same procedure as Example 1-l to obtain 187㎎ of the title compound as a colorless liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.55(s, 1H), 7.40(s, 2H), 3.50(m, 1H), 3.25(m, 2H), 2.85(m, 2H), 2.35-1.85(m, 8H), 1.65(m, 1H)

i) Synthesis of 3-methyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]benzo[b]furan-6-carbonitrile:

185㎎ of the compound obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 161㎎ of the colorless foamy solid product, which was then treated according to the same procedure as Example 1-l) to obtain 100㎎ of the title compound as a colorless foamy solid.

j) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-3-methylbenzo[d]-furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

100㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-m) to obtain 61㎎ of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65(s, 1H), 7.45(s, 2H), 4.20-4.0(m, 3H), 3.90 (m, 1H), 3.50(m, 2H), 3.15(m, 1H), 2.80(m, 3H), 2.15(s, 3H), 2.10-1.60(m, 12H), 1.20(t, 3H, J=7.19Hz)

k) Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-3-methylbenzo[d]-furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

60㎎ of the compound obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 2.9㎎ of the title compound as a colorless foamy solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.65(m, 1H), 7.45(m, 2H), 4.80(br, 3H), 4.20-4.0 (m, 3H), 3.85(m, 1H), 3.50(m, 4H), 3.15(m, 1H), 2.80(m, 3H), 2.15(s, 3H), 2.10-1.60(m, 10H), 1.20(t, 3H, J=7.19Hz)
ES-MS : 456(M+2)$^+$

Example 149 : Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo[b]thiophene-5-carboxamidine (Compound 253)

a) Synthesis of 5-bromo-2-((dimethylamino)thioxomethoxy)benzaldehyde:

In a 500㎖ flask, 35.6g of 5-bromosalicyl aldehyde was dissolved in 150㎖ of acetone, and 29.38g of anhydrous potassium carbonate was added. Thereafter, 21.9g of N,N-dimethylthiocarbamoyl chloride was slowly added, and the reaction solution thereby obtained was then stirred for 2 hours, poured into ice-water and then stirred. The resulting precipitate was filtered and washed three times with water. The filtered solid product was dried and then recrystallized from ethyl acetate/n-hexane(1:3) solvent system to obtain 42.3g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 10.03(s, 1H), 8.01(m, 1H), 7.72(m, 1H), 7.02(m, 1H), 3.47(s, 3H), 3.42(s, 3H)
ES-MS : 311(M+Na^+), 289(M+1)$^+$

b) Synthesis of N,N-dimethyl(4-bromo-2-formylphenylthio)formamide:

In a 100㎖ flask, 42.3g of 5-bromo-2-((dimethylamino)thioxomethoxy)benzaldehyde was introduced, melted for 10 minutes in oil bath at

210-220℃ and then dissolved in 30㎖ of toluene. After 100㎖ of methanol was added, the resulting precipitate was filtered, washed several times with n-hexane and then dried to obtain 12.3g of the title compound as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 10.25(s, 1H), 8.13(m, 1H), 7.70(m, 1H), 7.31(m, 1H), 3.15(s, 3H), 3.03(s, 3H)

Mass : 311($M+Na^+$), 289$(M+1)^+$

c) Synthesis of 1-(5-bromobenzo[b]thiophen-2-yl)ethan-1-one:

In a 100㎖ flask, 12.3g of N,N-dimethyl(4-bromo-2-formylphenylthio)formamide was dissolved in 35㎖ of methyl orthoformate, and 0.6g of p-toluenesulfonate was added. The reaction solution was stirred for 50 minutes at refluxing temperature and then cooled, and saturated $NaHCO_3$ solution was added. The organic layer was then extracted three times with benzene. After the extract was evaporated to remove the solvent, the residue was dissolved in 60㎖ of methanol, and 20㎖ of 2N-NaOH was added thereto. The reaction solution was refluxed under nitrogen atmosphere for one hour, cooled, adjusted to pH 1 with concentrated hydrochloric acid, and then extracted with benzene. After the solvent was removed from the extract, the residue was dissolved in 13㎖ of acetone. To the resulting solution was slowly added 3.5g of chloroacetone at room temperature. 1.3g of anhydrous potassium carbonate and 90㎖ of acetone were slowly added thereto. The reaction solution was stirred for 30 minutes at room temperature, refluxed again for 30 minutes, cooled and then filtered to remove the unsoluble material. The filtrate was evaporated and then purified with silica gel column chromatography [eluent : ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 1.66g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.03(m, 1H), 7.85(s, 1H), 7.75(m, 1H), 7.54(m, 1H), 2.66(s, 3H)

d) Synthesis of 5-bromobenzo[b]thiophene-2-carboxylic acid:

1.25㎖ of bromine was slowly added to 10㎖ of 5N aqueous NaOH solution with stirring and the resulting solution was cooled to -5℃-0℃. At the same temperature, a solution of 1.66g of 1-(5-bromobenzo[b]-thiophene-2-yl)ethan-1-one in 15㎖ of 1,4-dioxane was slowly added thereto. The reaction solution was stirred for 30 minutes at room temperature and then for 30 minutes at 50℃, cooled, poured into ice-water and then adjusted to pH 2 with concentrated hydrochloric acid. The resulting precipitate was filtered, washed several times with water, dried and then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and evaporated to obtain 1.42g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.03(m, 1H), 7.92(s, 1H), 7.76(m, 1H), 7.50(m, 1H)

e) Synthesis of ethyl 5-bromobenzo[b]thiophene-2-carboxylate:

In a 100㎖ flask, 1.42g of 5-bromobenzo[b]thiophene-2-carboxylic acid and 25㎖ of methanol were introduced and then stirred. The resulting suspension was cooled in ice bath and 0.6㎖ of thionyl chloride was slowly added thereto. The reaction solution was refluxed for one hour and then cooled. After 1.1㎖ of thionyl chloride was added, the reaction solution was refluxed for further 2 hours, cooled and then adjusted to pH 9 with saturated $NaHCO_3$ solution. The resulting precipitate was filtered, dried and then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 1.3g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.01(m, 1H), 7.96(s, 1H), 7.73(m, 1H), 7.54(m, 1H), 4.41(q, 2H, J=7.0Hz), 1.42(t, 3H, J=7.0Hz)

f) Synthesis of ethyl 5-cyanobenzo[b]thiophene-2-carboxylate:

In a 50㎖ flask, 1.3g of 5-bromobenzo[b]thiophene-2-carboxylate and 1.02g of CuCN were introduced and 20㎖ of N-methyl-2-pyrrolidone was then added thereto. The mixture was stirred and the resulting suspension was refluxed under nitrogen atmosphere for 2 hours at 200℃. The reaction solution was cooled, poured into ice-water, vigorously stirred and then filtered to remove the unsoluble material. The filtrate was then extracted with ethyl acetate. The extract was evaporated to remove the solvent, and the residue was then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and evaporated to obtain 330㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.21(m, 1H), 8.09(s, 1H), 7.97(m, 1H), 7.70(m, 1H), 4.45(q, 2H, J=7.0Hz), 1.43(t, 3H, J=7.0Hz)

g) Synthesis of 2-(hydroxymethyl)benzo[b]thiophene-5-carbonitrile:

220㎎ of the compound obtained in the above f) was treated according to the same procedure as Example 1-e) to obtain 120㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.03(m, 1H), 7.90(m, 1H), 7.51(m, 1H), 7.26(s, 1H), 4.97(s, 2H)

h) Synthesis of (5-cyanobenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide:

120㎎ of the compound obtained in the above g) was treated according to the same procedure as Example 1-f) to obtain 215㎎ of the title compound as a yellowish white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.09-7.27(m, 19H), 6.70(s, 2H)

i) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[b]thiophen-2-yl)vinyl]-

pyrrolidine carboxylate:

211㎎ of (5-cyanobenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide obtained in the above h) was reacted according to the same procedure as Example 1-j) to obtain 150㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.01(m, 1H), 7.81(m, 1H), 7.48(m, 1H), 7.14(s, 1H), 6.69-6.49(m, 1H), 6.13-6.05(m, 1H), 4.57-4.32(m, 1H), 3.42 (m, 2H), 2.38-1.73(m, 4H), 1.48(brs, 9H)
ES-MS : 377($M+Na^+$), 355$(M+1)^+$

j) Synthesis of tert-butyl (S)-[2-(5-cyanobenzo[b]thiophen-2-yl)ethyl]-pyrrolidine carboxylate:

155㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-k) to obtain 130㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.93(m, 1H), 7.82(m, 1H), 7.41(m, 1H), 7.08(s, 1H), 3.90(brs, 1H), 3.52-3.27(m, 2H), 2.89(m, 2H), 2.35-1.65(m, 6H), 1.41(brs, 9H)
ES-MS : 379($M+Na^+$), 357$(M+1)^+$

k) Synthesis of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]thiophene-5-carbonitrile:

128㎎ of the compound obtained in the above j) was treated according to the same procedure as Example 1-l) to obtain 72㎎ of the title compound as a white solid.

l) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo-[b]thiophene-5-carbonitrile:

72㎎ of the compound obtained in the above k) and phenylacetyl chloride were reacted according to the same procedure as Example 1-m)

to obtain 55㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.94(m, 1H), 7.80(m, 1H), 7.43(m, 1H), 7.36-7.23 (m, 5H), 7.11(s, 1H), 4.22(m, 1H), 3.66(m, 2H), 3.48(m, 2H), 2.93(m, 2H), 2.39-1.75(m, 6H)

ES-MS : 397($M+Na^+$), 375$(M+1)^+$

m) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]- benzo -[b]thiophene-5-carboxamidine:

55㎎ of the compound obtained in the above l) was treated according to the same procedure as Example 1-n) to obtain 45㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.91(m, 1H), 7.75(m, 1H), 7.46(m, 1H), 7.32-7.13 (m, 5H), 7.07(s, 1H), 4.23(m, 1H), 3.66-3.58(m, 2H), 3.48(m, 2H), 2.89(m, 2H), 2.38-1.75(m, 6H)

ES-MS : 392$(M+1)^+$

IR(KBr) : 3079, 2954, 1613 cm^{-1}

Example 150 : Synthesis of 3-methoxy-2-[2-[(S)-1-(2-phenyl-acetyl)pyrrolidin-2-yl]ethyl]benzo[b]thiophene-6-carboxamidine (Compound 255)

a) Synthesis of prop-2-enyl 3-nitro-4-(prop-2-enoxycarbonyl)benzoate:

In a 500㎖ flask, 25g of 2-nitrobenzene-1,4-dicarboxylic acid and 21.88g of $NaHCO_3$ were dissolved in 150㎖ of N,N-dimethylformamide. To the resulting solution was slowly added 25.6㎖ of allyl bromide. The reaction solution was stirred for 3 hours at 50℃, cooled, adjusted to pH 6 with 2N-HCl and then extracted three times with ethyl acetate. The combined extract was dried and then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 34g of the title compound as a pale yellow liquid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.61(m, 1H), 8.33(m, 1H), 7.82(m, 1H), 6.14-5.94 (m, 2H), 5.49-5.32(m, 4H), 4.92-4.86(m, 4H)
ES-MS : 314($M+Na^+$)

b) Synthesis of methyl 3-hydroxy-6-(prop-2-enyloxycarbonyl)benzo[b]-thiophene-2-carboxylate:

In a 500mℓ flask, 34g of the compound obtained in the above a) and 15.66mℓ of methyl thioglycolate were dissolved in 150mℓ of N,N-dimethylformamide. The resulting solution was cooled in ice-bath and lithium hydroxide was added portionwise thereto. The reaction solution was stirred for 30 minutes under ice-bath and then for 2 hours at room temperature, poured into ice-water, treated with concentrated hydrochloric acid and then extracted three times with ethyl acetate. The combined extract was dried and purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:7)]. The fractions containing the desired product were combined and then evaporated to obtain 13.1g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 10.08(s, 1H), 8.52(s, 1H), 8.09-7.98(m, 2H), 6.12-6.01(m, 1H), 5.49-5.33(m, 2H), 4.89(m, 2H), 3.97(s, 3H)
ES-MS : 315($M+Na^+$), 293$(M+1)^+$

c) Synthesis of 3-hydroxy-2-(methoxycarbonyl)benzo[b]thiophene-6-carboxylic acid:

In a 500mℓ flask, 22.8g of the compound obtained in the above b) and 32.8g of dimedone were dissolved in 150mℓ of tetrahydrofuran, and 4.5g of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] was added thereto. The reaction solution was stirred for 3 hours at room temperature. The resulting precipitate was filtered, washed several times with ethyl acetate and then dried in air to obtain 18.2g of the title compound as a white solid.

^{1}H NMR(DMSO-d_6, ppm) : δ 8.56(s, 1H), 8.01-7.91(m, 2H), 3.87(s, 3H)

d) Synthesis of methyl 6-carbamoyl-3-hydroxybenzo[b]thiophene-2-caboxylate:

In a 100mℓ flask, 18.2g of the compound obtained in the above c) was dissolved in 40mℓ of thionyl chloride. The resulting solution was refluxed for 30 minutes, cooled and then distilled under reduced pressure to remove thionyl chloride. The remaining thionyl chloride was removed for 5 hours by means of a vaccum pump. To the dried product was slowly added 40mℓ of NH_4OH at 0℃. The reaction solution was stirred for 4 hours at room temperature, and the resulting precipitate was filtered, washed several times with ethyl acetate and then dried to obtain 17.5g of the title compound as a white solid.

^1H NMR(DMSO-d_6, ppm) : δ 8.17(s, 1H), 7.98(brs, 1H), 7.79-7.69(m, 2H), 7.30(brs, 1H), 3.69(s, 3H)

e) Synthesis of methyl 6-cyano-3-hydroxybenzo[b]thiophene-2-caboxylate

In a 500mℓ flask, 17.5g of the compound obtained in the above d) was dissolved in 50mℓ of tetrahydrofuran, and a solution of 54.8g of triphenylphosphine in 100mℓ of carbon tetrachloride was slowly added. The reaction solution was stirred for 30 minutes at room temperature and then for one day at 60℃, cooled and filtered to remove the unsoluble material. The filtrate was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and evaporated to obtain 457mg of the title compound as a pale pink solid.

^1H NMR($CDCl_3$, ppm) : δ 10.14(s, 1H), 8.06-7.99(m, 2H), 7.62(m, 1H), 3.99(s, 3H)

ES-MS : 489($2M+Na^+$), 256($M+Na^+$)

f) Synthesis of methyl 6-cyano-3-methoxybenzo[b]thiophene-2-carboxylate:

In a 50㎖ flask, 227㎎ of the compound obtained in the above e) was dissolved in 10㎖ of N,N-dimethylformamide, and 47㎎ of NaH was added thereto at 0℃. To this mixture was slowly added 0.15㎖ of methyliodide. The reaction solution was stirred for 4 hours at 60℃ and ice-water was then added. This solution was extracted three times with dichloromethane. The extract was dried and purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and evaporated to obtain 153㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.08(m, 1H), 7.95(m, 1H), 7.59(m, 1H), 4.22(s, 3H), 3.97(s, 3H)

ES-MS : 270($M+Na^+$)

g) Synthesis of 2-(hydroxymethyl)-3-methoxybenzo[b]thiophene-6-carbonitrile:

260㎎ of the compound obtained in the above f) was treated according to the same procedure as Example 1-e) to obtain 176㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.06(m, 1H), 7.79(m, 1H), 7.58(m, 1H), 4.97(s, 2H), 4.01(s, 3H)

ES-MS : 461($2M+Na^+$), 242($M+Na^+$)

h) Synthesis of (6-cyano-3-methoxybenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide:

176㎎ of the compound obtained in the above g) was treated according to the same procedure as Example 1-f) to obtain 340㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 7.91-7.52(m, 18H), 5.89(m, 2H), 3.89(s, 3H)

i) Synthesis of tert-butyl (S)-[2-(6-cyano-3-methoxybenzo[b]thiophen-2-yl)vinyl]pyrrolidine carboxylate:

335㎎ of (6-cyano-3-methoxybenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide obtained in the above h) was treated according to the same procedure as Example 1-j) to obtain 230㎎ of the title compound as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 8.00(m, 1H), 7.76(m, 1H), 7.57(m, 1H), 6.78(m, 1H), 6.10-5.77(m, 1H), 4.96(m, 1H), 3.95(s, 3H), 3.48(m, 2H), 2.38-1.74(m, 4H), 1.42(m, 9H)

j) Synthesis of tert-butyl (S)-[2-(6-cyano-3-methoxybenzo[b]thiophen-2-yl)ethyl]pyrrolidine carboxylate:

230㎎ of the compound obtained in the above i) was treated according to the same procedure as Example 1-k) to obtain 233㎎ of the title compound as a white solid.

^{1}H NMR($CDCl_3$, ppm) : δ 8.01(m, 1H), 7.72(m, 1H), 7.51(m, 1H), 3.92(s, 3H), 3.57-3.28(m, 3H), 2.86(m, 2H), 2.28-1.66(m, 6H), 1.43(m, 9H)

ES-MS : 409($M+Na^+$)

k) Synthesis of 3-methoxy-2-[((S)-2-pyrrolidin-2-yl)ethyl]benzo[b]thiophene-6-carbonitrile:

230㎎ of the compound obtained in the above j) was treated according to the same procedure as Example 1-l) to obtain 39㎎ of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.97(m, 1H), 7.71(m, 1H), 7.55(m, 1H), 3.90(s, 3H), 3.58(m, 1H), 3.47-3.29(m, 2H), 3.08(m, 2H), 2.50-1.80(m, 6H)

ES-MS : 287($M+1)^+$

l) Synthesis of 3-methoxy-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]benzo[b]thiophene-6-carbonitrile:

39㎎ of the compound obtained in the above k) and phenylacetyl cloride were reacted according to the same procedure as Example 1-m) to obtain 18㎎ of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$, ppm) : δ 7.98(m, 1H), 7.68(m, 1H), 7.48(m, 1H), 7.23(m, 5H), 4.24(m, 1H), 3.89(s, 3H), 3.65(m, 2H), 3.47(m, 2H), 2.88(m, 2H), 2.32-1.65(m, 6H)

ES-MS : 427($M+Na^+$), 405$(M+1)^+$

m) Synthesis of 3-methoxy-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]benzo[b]thiophene-6-carboxamidine:

18㎎ of the compound obtained in the above l) was treated according to the same procedure as Example 1-n) to obtain 10㎎ of the title compound as a pale yellow solid.

^{1}H NMR($CDCl_3$) : δ 7.97(m, 1H), 7.68-7.52(m, 2H), 7.26-6.98(m, 5H), 4.16 (m, 1H), 3.87(s, 3H), 3.65(m, 2H), 3.44(m, 2H), 2.87(m, 2H), 2.26-1.58(m, 6H)

ES-MS : 422$(M+1)^+$

IR(KBr) : 2992, 1612, 1460 cm^{-1}

Example 151 : Synthesis of N-methyl [3-[[(S)-2-[2-[6-[imino-(methylamino)methyl]-1-methylindol-2-yl]ethyl]pyrrolidinyl]methyl]-benzo[b]thiophen-2-yl]formamide (Compound 258)

68㎎ of 1-methyl-2-[2-[(S)-1-[[2-(N-methylcarbamoyl)benzo[b]-thiophene-3-yl]methyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine obtained in Example 10 was dissolved in 10㎖ of 40% methylamine methanol solution and then stirred overnight at room temperature. The reaction solution was distilled under reduced pressure to remove the reaction solvent and the residue was purified with column chromatography [eluent: dichloromethane/methanol(10:1)] on NH-DM1020 silica. The fractions containing the desired product were combined and distilled under reduced pressure to obtain 52㎎ of the title compound as a pale

yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.91(d, 1H), 7.84(d, 1H, J=6.54Hz), 7.67(s, 1H), 7.52(d, 1H), 7.39-7.31(m, 3H), 6.15(s, 1H), 4.12(d, 1H), 3.83(d, 1H), 3.62(s, 3H), 3.05(s, 3H), 2.99(s, 1H), 2.85(m, 1H), 2.77-2.70(m, 2H), 2.41(m, 1H), 2.19(m, 1H), 2.05(m, 1H), 1.79-1.58(m, 4H)

Example 152 : Synthesis of 1-[(S)-2-[2-(6-[(hydroxyimino)amino-methyl]-1-ethylindol-2-yl]ethyl]pyrrolidinyl]-2-phenylethan-1-one (Compound 260)

190㎎ of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile obtained in Example 14-a) was dissolved in methanol. 103㎎ of hydroxylamine hydrochloride and 210㎎ of sodium carbonate were added and the reaction solution was refluxed overnight with stirring. After water was added, the reaction solution was extracted two times with dichloromethane. The extract was dried over $MgSO_4$ and distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol (20:1)] to obtain 11㎎ of the title compound.

^{1}H NMR(MeOH-d_4) : δ 7.52(s, 1H), 7.34(d, 1H, J=8.38Hz), 7.27-6.80(m, 6H), 6.18(s, 1H), 4.08(m, 3H), 3.60(d, 2H, J=5.36Hz), 3.44(m, 2H), 2.66(t, 2H, J=8.00Hz), 2.13(m, 1H), 1.92-1.60(m, 6H), 1.21(t, 3H, J=7.15Hz)

ES-MS : 419$(M+1)^+$, 441(M+Na)

Example 153 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-[6-[(hydroxyimino)aminomethyl]-1-ethylindol-2-yl]ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 261)

480㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60-a) was dissolved in methanol. 304㎎ of hydroxylamine hydrochloride and

695㎎ of sodium carbonate were added and the reaction solution was refluxed overnight with stirring. After water was added, the reaction solution was extracted two times with dichloromethane. The extract was dried over $MgSO_4$ and distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 27㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.53(s, 1H), 7.35(d, 1H, J=8.25Hz), 7.21(d, 1H, J=4.43Hz), 6.21(s, 1H), 4.11(m, 3H), 3.99(m, 2H), 3.68(t, 1H), 3.49(m, 2H), 3.34(d, 2H, J=18.9Hz), 3.12(m, 1H), 2.68(m, 2H), 2.25-1.60(m, 11H), 1.25(t, 3H), 1.10(t, 3H)

ES-MS : 482$(M+1)^+$

Example 154 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-[1-ethyl-6-[(acetylamino)iminomethyl]indol-2-yl]ethyl]pyrrolidinyl]carbonyl]-pyrrolidinyl]acetate (Compound 265)

52㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was dissolved in dry dichloromethane. To the resulting solution was added 31㎕ of triethylamine, and the mixture was cooled to -78℃. After 16㎕ of acetyl chloride was added, the reaction solution was stirred for 3 hours and warmed to room temperature. Water was added and the mixture was extracted with dichloromethane. The extract was dried over $MgSO_4$ and evaporated under reduced pressure to remove the solvent. The residue was purified with silica gel column chromato- graphy [eluent: ethyl acetate/methanol(50:1)] to obtain 7㎎ of the title compound as a pale yellow solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.72(s, 1H), 7.44(d, 1H, J=8.00Hz), 7.29(d, 1H, J=8.27Hz), 6.28(s, 1H), 4.17(m, 3H), 4.02(m, 2H), 3.70(m, 1H), 3.49(m, 4H), 3.33(d, 2H, J=20.26Hz), 3.09(m, 1H), 2.75(m, 2H), 2.64(m, 1H), 2.30-1.60(m, 8H), 1.25(t, 3H), 1.19(s, 3H), 1.07(t, 3H)

Example 155 : Synthesis of N-[[1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]indol-6-yl]iminomethyl]ethoxyformamide (Compound 266)

170㎎ of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine obtained in Example 14 was dissolved in dichloromethane. 90㎕ of triethylamine and 70㎎ of ethyl chloroformate were added at 0℃. The reaction solution was stirred for one hour at room temperature and distilled under reduced pressure to remove the reaction solvent. The residue was purified with column chromatography [eluent: ethyl acetate] on NH-DM1020 silica. The fractions containing the desired product were combined and distilled under reduced pressure to obtain 110㎎ of the title compound as a white solid.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.34(s, 1H), 7.49(d, 1H), 7.42(m, 1H), 7.38-7.22(m, 5H), 6.36(s, 1H), 4.34-4.22(m, 6H), 3.66(s, 2H), 3.50(m, 3H), 2.77(m, 2H), 2.33(m, 1H), 1.98(m, 5H), 1.74(m, 3H), 1.37(m, 6H)

Example 156 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-[1-ethyl-6-[(ethoxycarbonylamino)iminomethyl]indol-2-yl]ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]acetate (Compound 267)

200㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl]-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was dissolved in dichloromethane and then cooled to 0℃. 119㎕ of triethylamine was added and after 30 minutes, 49㎕ of ethyl chlorocarbonate was added. After one hour, water was added to the reaction solution, which was then extracted two times with dichloromethane. The combined extract was dried over $MgSO_4$ and then concentrated. The residue was subjected to column chromatography [eluent: ethyl acetate] on NH-DM1020 silica to obtain 124㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.03(s, 1H), 7.20(s, 1H), 6.40(s, 1H), 4.35-4.05(m, 7H), 3.81(q, 1H), 3.74-3.34(m, 4H), 3.25(m, 1H), 2.85(m,

2H), 2.77(m, 1H), 2.40-1.70(m, 10H), 1.35(m, 6H), 1.22(m, 3H)

Example 157 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-[1-ethyl-6-[imino[(methylethoxy)carbonylamino]methyl]indol-2-yl]ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 270)

200㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was reacted with 67㎕ of isobutylchloroformate according to the same procedure as Example 154 to obtain 195㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.91(s, 1H), 7.42(m, 2H), 6.32(s, 1H), 4.18(m, 3H), 3.75(d, 2H, J=6.66Hz), 3.67(t, 1H), 3.50(m, 3H), 3.30(d, 2H), 3.08(m, 1H), 2.74(m, 2H), 2.62(q, 1H), 2.30-1.60(m, 12H), 1.28(t, 3H), 1.08(t, 3H), 0.92(d, 6H)

Example 158 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-[6-[[(trichloromethoxy)carbonylamino]iminomethyl]-1-ethylindol-2-yl]-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 272)

100㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was reacted with 35㎕ of trichloroethylchloroformate treated according to the same procedure as Example 154 to obtain 92㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 7.97(s, 1H), 7.46(m, 2H), 6.29(s, 1H), 4.81(s, 2H), 4.18(m, 3H), 3.67(t, 1H), 3.57-3.05(m, 7H), 2.76(m, 2H), 2.64(q, 1H), 2.30-1.60(m, 10H), 1.27(t, 3H), 1.07(t, 3H)

Example 159 : Synthesis of ethyl 2-[(R)-2-[[(S)-2-[2-[1-ethyl-6-[imino(phenylcarbonylamino)methyl]indol-2-yl]ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]acetate (Compound 273)

60㎎ of ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was

reacted with 24㎕ of benzylchloroformate according to the same procedure as Example 154 to obtain 64㎎ of the title compound.

^{1}H NMR(MeOH-d_4, ppm) : δ 8.10-6.60(m, 8H), 6.30(s, 1H), 4.16(m, 3H), 4.00(m, 2H), 3.65(m, 1H), 3.49(m, 2H), 3.34(d, 2H, J= 19.08Hz), 3.11(m, 1H), 2.75(m, 2H), 2.66(q, 1H), 2.40-1.60(m, 10H), 1.26(t, 3H), 1.11(t, 3H)

ES-MS : 588(M+1)$^+$

Test 1 : Inhibitory activity for thrombin and trypsin

20㎕ of each compound of the present invention was dissolved in 50% methanol in various concentrations and then added to each well of a microplate, to each of which 160㎕ of the reaction medium containing 125mM NaCl, 50mM Tris-HCl (pH 8.0) and 2mM synthetic substrate (N-benzoyl-Phe-Val-Arg-p-nitroanilide, Sigma B-7632) were added. 20 ㎕ of human thrombin solution (5 units/㎖, Sigma T-6759, manufactured by Sigma Co.) containing 0.1% bovine serum albumin was added to each well to initiate the enzymatic reaction. After 20 minutes, the hydrolysis of substrate was determined by measuring the absorbance at 405㎚. The concentration of the test compound showing half the change of the absorbance in the well that did not contain the test compound was represented as IC_{50} value. The selectivity index was calculated by dividing the IC_{50} value for trypsin by the IC_{50} value for thrombin. The thrombin inhibitory activity and the trypsin inhibitory activity for the compound of the present invention are shown in the following Table 2.

Table 2. Inhibitory activity for thrombin and trypsin

Compound No.	Inhibitory activity (IC_{50})		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
8	9.47	460.0	48.6
9	33.9		
15	20.1	608.0	30.2
24	8.45	706.0	83.6
30	9.01	420.0	46.6
37	5.40		
38	7.59	184.0	24.2
39	6.91		
40	7.95		
43	9.96	401.0	40.3
44	9.23	313.0	33.9
46	28.9		
57	7.73		
58	3.00	52.2	17.4
62	11.7	582.0	49.7
64	15.2	349.0	22.9
65	22.1		
72	9.4	128.0	13.6
73	33.2	268.0	
83	30.9		
84	51.6	4490.0	87.0
86	27.0	674.0	25.0
88	15.9	128.0	8.1

Table 2. (continued)

Compound No.	Inhibitory activity (IC_{50})		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
98	20.3		
109	31.9		
110	37.7	1460.0	38.6
112	29.2		
114	17.4	500.0	28.8
115	31.8		
116	31.7	869.0	27.4
117	16.7	811.0	48.6
118	12.3	178.0	14.5
123	32.9		
125	22.3	775.0	34.7
126	40.5		
127	21.7		
128	26.2		
129	13.1	139.0	10.6
130	36.5		
131	9.29	137.0	14.7
142	33.1		
143	5.46	410.0	75.2
144	25.3		
145	26.1	524.0	20.1
146	22.1	464.0	21.0
147	25.5		

Table 2. (continued)

Compound No.	Inhibitory activity (IC_{50})		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
148	23.0	443.0	19.2
149	10.4		
155	11.6	287.0	24.7
156	28.6		
157	26.9		
158	5.50		
159	19.3	399.0	20.7
160	15.3	382.0	25.0
161	5.21	255.0	48.9
162	7.3	329.0	45.0
163	19.4	497.0	25.6
166	33.1	617.0	18.6
167	18.3	322.0	17.6
168	31.6		
169	30.2		
170	33.5	1070.0	31.9
171	10.6	373.0	35.1
173	34.6		
174	16.2	416.0	25.7
175	9.92		
176	21.7	450.0	20.7
177	18.8	500.0	26.6
180	11.0	351.0	31.8

Table 2. (continued)

Compound No.	Inhibitory activity (IC_{50})		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
182	10.1	304.0	30.0
184	9.51	551.0	57.9
187	25.6		
192	33.8		
194	31.7		
196	37.2	536.0	14.4
222	11.4		
224	24.1		
244	53.6		

Test 2 : Measurement of the thrombin time (TT) in rat plasma

SD male rats weighing 220±20g which had fasted overnight were used as experimental animals. Blood taken from the hearts of the experimental animals just before administration of the test compound and at 30, 60, 120 and 240 minutes after oral administration of the test compound was mixed with 0.108M sodium citrate in the ratio of 9:1. The mixtures thereby obtained were centrifuged at 15,000rpm for 5 minutes at 4℃ to separate the plasma, which was stored at -20℃ until the TT was measured by means of the method described below.

200㎕ of Owren's buffer was added to 50㎕ of the plasma and 100 ㎕ of the diluted plasma thereby obtained was injected into the vial of a coagulometer and then incubated for 2 minutes at 37℃. To each vial was added 100㎕ of thrombin at a concentration of 20U/㎖, which had prewarmed at 37℃, to measure the time (TT) until clotting occurred.

The ratio of the TT in rat plasma after administration of the test compound to the TT in rat plasma before administration of the test compound was calculated. The TT ratios for the compounds of the present invention are shown in the following Table 3.

Table 3. Plasma TT ratio after administration to rat

Compound No. \ Dosage	30mg/kg	50mg/kg	100mg/kg
86	1.49	4.51	5.19
88	2.62	7.83	
118		8.80	
126		5.40	
127		8.00	
149		9.24	
155		3.93	7.36
159		6.23	
160		2.30	
161		7.62	
171			4.23
267		4.48	
270	1.46	4.30	
272	1.76	2.84	

Test 3 : Pharmacokinetic test

Test method :

S.D. male rats weighing 200±20g which had fasted overnight were subjected to cannulation at their femoral veins and arteries.

Compound 88 prepared in Example 62 was dissolved in physiological saline and then administered to the rats both by intravenous injection and oral administration. Blood was taken at prescribed intervals of time and then immediately mixed with methanol The mixture was centrifuged (15,000rpm, 5 min., 4℃) to obtain quantitative amount of the supernatant which was then subjected to HPLC in Diode Array Detector at 254㎚ to analyse the concentration of the test compound in the blood.

Test results :

The blood concentrations of compound 88 according to the present invention analysed after intravenous injection and oral administration are shown in the following Tables 4 and 5, and the pharmacokinetic parameter is described in the following Table 6. As can be seen from the experimental results shown in these tables, when compound 88 of the present invention was administered via intravenous injection, it was rapidly distributed in the body and slowly disappeared. In rats, compound 88 of the present invention exhibited a good result, i.e. an elimination half-time of 64 minutes and a bioavailability of 32.6%.

Table 4. Blood concentration of the compound 88 of example 62 following intravenous injection of 10㎎/㎏ in rats

Time (h)	Blood concentration (㎍/㎖)						
	Rat-1	Rat-2	Rat-3	Rat-4	Rat-5	Mean	SE
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.033	11.186	25.999	23.841	28.971	18.505	21.700	1.975
0.083	8.793	11.984	10.776	14.222	11.623	11.480	0.658
0.250	2.707	4.629	3.531	5.982	3.895	4.149	0.484
0.500	0.816	1.963	1.685	2.939	1.516	1.784	0.284
1.000	0.784	0.773	0.577	1.204	0.535	0.775	0.137
2.000	0.204	0.098	0.000	0.424	0.162	0.178	0.081
4.000	0.000	0.000	0.000	0.121	0.055	0.035	0.026
6.000	0.000	0.000	0.000	0.090	0.051	0.028	0.020
24.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 5. Blood concentration of the compound 88 of example 62 following oral administration of 100㎎/㎏ in rats

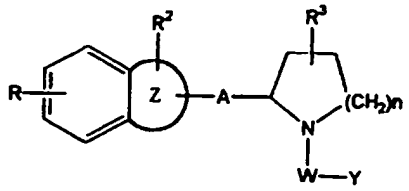
Time (h)	Blood concentration (㎍/㎖)						
	Rat-1	Rat-2	Rat-3	Rat-4	Rat-5	Mean	SE
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.033	11.186	25.999	23.841	28.971	18.505	21.700	1.975
0.083	8.793	11.984	10.776	14.222	11.623	11.480	0.658
0.250	2.707	4.629	3.531	5.982	3.895	4.149	0.484
0.500	0.816	1.963	1.685	2.939	1.516	1.784	0.284
1.000	0.784	0.773	0.577	1.204	0.535	0.775	0.137
2.000	0.204	0.098	0.000	0.424	0.162	0.178	0.081
4.000	0.000	0.000	0.000	0.121	0.055	0.035	0.026
6.000	0.000	0.000	0.000	0.090	0.051	0.028	0.020
24.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 6. Pharmacokinetic parameters of the compound 88 of Example 62 in rats

Parameter	Mean±error
Elimination Half-life (hr)	1.07±0.27
Bioavailability (%)	32.62±7.69

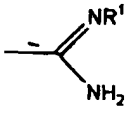
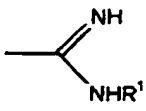
WHAT IS CLAIMED IS :

1. A compound represented by formula (I):

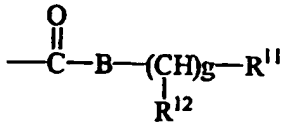


(I)

and pharmaceutically acceptable salts thereof, in which

R represents a group of formula  or  , wherein

R^1 represents hydrogen, hydroxy, alkyl, alkoxy, alkylcarbonyl, alkylcarbonyloxy, aralkoxycarbonyl, or a radical of formula (a),



(a)

wherein

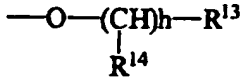
B represents oxygen or sulfur;

R^{11} and R^{12} independently of one another represent hydrogen, haloalkyl, alkylcarbonyloxy, dialkylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

g denotes an integer of 0 to 3;

R^2 represents hydrogen, hydroxy, halogen, carboxy, aminocarbonyl, alkyl, alkoxy, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkylsulfonyl, carboxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^3 represents hydrogen, halogen, alkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, carboxy, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, or a radical of formula (b),

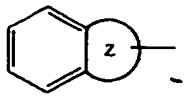


(b)

wherein

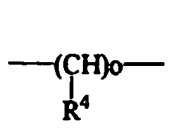
R^{13} and R^{14} independently of one another represent hydrogen, alkyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

h denotes an integer of 0 to 3;

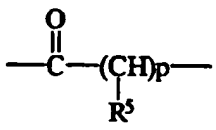
the group of formula  represents a radical selected from the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, naphthyl, tetrahydronaphthyl, indanyl, dihydrobenzofuranyl and dihydrobenzothienyl;

A represents a saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, alkoxycarbonyl and alkoxycarbonylalkyl;

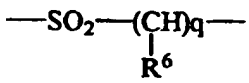
W represents a group of formula (c), (d) or (e),



(c)



(d)

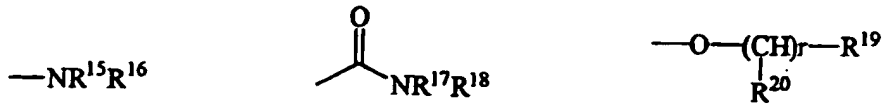


(e)

wherein

o, p and q independently of one another denote an integer of 0 to 3,

R^4, R^5 and R^6 independently of one another represent hydrogen, hydroxy, carboxy, alkoxycarbonyl, substituted or unsubstituted arylsulfonyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),



(f) (g) (h)

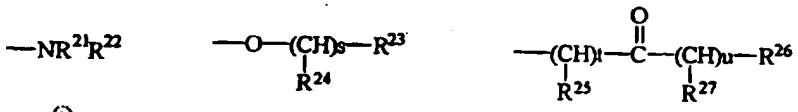
wherein

R^{15}, R^{16}, R^{17} and R^{18} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, aminocarbonylalkyl, alkoxycarbonylalkyl, substituted or unsubsituted arylsulfonyl, substituted or unsubstituted aralkyl, or substituted or unsubsituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or alkoxycarbonyl, or represents 3- to 7-memebered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings; and

r denotes an integer of 0 to 3;

Y represents hydrogen or a 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings and which may be substituted on any atom of the ring with a substituent selected from the group consisting of oxygen, halogen, nitro, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



(i) (j) (k)

wherein

R^{21} and R^{22} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, alkoxycarbonyl, or 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings;

R^{25}, R^{26} and R^{27} independently of one another represent hydrogen, hydroxy, thio, amino, carboxy, aminocarbonyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfonylamino, alkenyl, alkoxycarbonylamino, cycloalkylamino, alkoxycarbonylalkylamino, substituted or unsubstituted arylsulfonylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

s denotes an integer of 0 to 3;

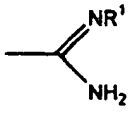
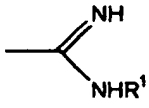
t denotes an integer of 0 to 6; and

u denotes an integer of 0 to 8; and

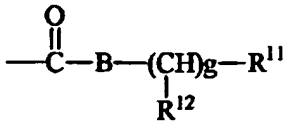
n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be straight or branched.

2. The compound as defined in claim 1, wherein

R represents a group of formula  or  , wherein

R^1 represents hydrogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_4 alkylcarbonyl, C_2-C_4 alkylcarbonyloxy, or a radical of formula (a),

 (a)

wherein

B represents oxygen or sulfur,

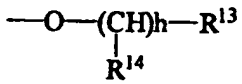
R^{11} and R^{12} independently of one another represents hydrogen, C_1-C_4

haloalkyl, C_2-C_4 alkylcarbonyloxy, C_2-C_6 dialkylamino, or substituted or unsubstituted 6-membered carbocyclic ring, and

g denotes an integer of 0 to 3;

R^2 represents hydrogen, halogen, carboxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 aminoalkyl, C_2-C_4 alkylcarbonyl, C_1-C_4 alkylsulfonyl, C_2-C_4 carboxyalkyl, C_2-C_4 aminocarbonylalkyl or C_3-C_7 alkoxycarbonylalkyl;

R^3 represents hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_2-C_4 carboxyalkyl, C_3-C_7 alkoxycarbonylalkyl, or a radica of formula (b),

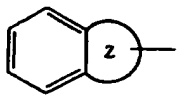


(b)

wherein

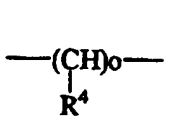
R^{13} and R^{14} independently of one another represent hydrogen or phenyl, and

h denotes an integer of 0 to 1;

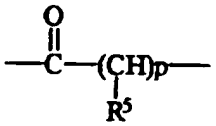
the group of formula  represents a radical selected from the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl and naphthyl;

A represents saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, C_1-C_4 hydroxyalkyl and C_2-C_4 alkoxycarbonyl;

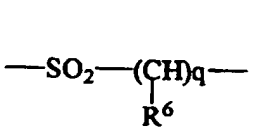
W represents a group of formula (c), (d) or (e),



(c)



(d)

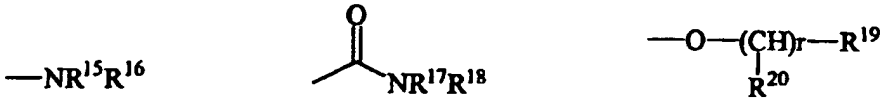


(e)

wherein

o, p and q independently of one another denote an integer of 0 to 3,

R^4, R^5 and R^6 independently of one another represent hydrogen, hydroxy, carboxy, C_2-C_4 alkoxycarbonyl, phenylsulfonyl, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),



(f) (g) (h)

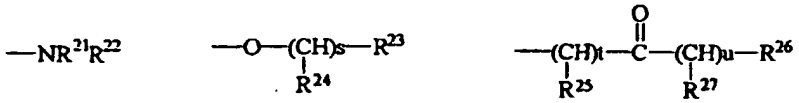
wherein

R^{15}, R^{16}, R^{17} and R^{18} independently of one another represent hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylsulfonyl, C_2-C_4 carboxyalkyl, C_2-C_4 alkylcarbonyl, C_2-C_4 aminocarbonylalkyl, C_3-C_7 alkoxycarbonylalkyl, or substituted or unsubsituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or C_2-C_4 alkoxycarbonyl, or represents 5- to 6-memebered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring, and

r denotes an integer of 0 to 3;

Y represents hydrogen, or represents 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring and which can be substituted on any atom of the ring with substituent selected from the group consisting of oxygen, halogen, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkylsulfonyl, phenylsulfonyl, substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



(i) (j) (k)

wherein

R^{21} and R^{22} independently of one another represent hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylsulfonyl, C_2-C_5 carboxyalkyl, C_2-C_5 alkylcarbonyl, C_3-C_7 alkoxycarbonylalkyl or phenylsulfonyl,

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, C_2-C_4 alkoxycarbonyl, or 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

R^{25}, R^{26} and R^{27} independently of one another represents hydrogen hydroxy, thio, amino, carboxy, aminocarbonyl, C_1-C_4 alkoxy, C_2-C_4 alkoxycarbonyl, C_1-C_4 alkylamino, C_1-C_4 alkylsulfonylamino, C_2-C_5 alkenyl, C_2-C_4 alkoxycarbonylamino, C_3-C_6 alkoxycarbonylalkylamino, C_3-C_6 cycloalkylamino, phenylsulfonylamino, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

s denotes an integer of 0 to 3,

t denotes an integer of 0 to 6, and

u denotes an integer of 0 to 8, and

n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be strainght or branched.

3. The compound as defined in claim 1, which is selected from the group consisting of:

3-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]-benzo[b]thiophene-2-carboxamide,

3-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]-benzo[b]thiophene-2-carboxamide,

1-ethyl-2-[2-[(S)-1-[2-(3-chlorophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid,

1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]-

indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfonylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate,
1-ethyl-2-[2-[(S)-1-[(R)-2-(carbamoylmethylamino)-2-phenylacetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
2-[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetic acid,
1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate,
1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[2-[cyclopropyl(methylsulfonyl)amino]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate,
ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate,
2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetic acid,
ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopropylamino-4-oxobutanoate,
4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine,
ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate,
ethyl 2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]acetate,

2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]acetic acid,

2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methyl-pyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid,

ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]propionate,

ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]butanoate,

ethyl-2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-2-phenylacetate,

1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[[(R)-1-[(N-cyclopropylcarbamoyl)methyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl (S)-2-[2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyr-rolidinyl]carbonyl]pyrrolidinyl]acetylamino]propanoate,

1-ethyl-2-[2-[(S)-1-[[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

2-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]car-bonyl]pyrrolidinyl]-4-hydroxybutanoic acid,

1-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]car-bonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid,

1-ethyl-2-[2-[(S)-1-[[1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrro-lidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]butanoate,

4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]butanoic acid,

ethyl 5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]pentanoate,

5-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]pentanoic acid,

ethyl 6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]hexanoate,

6-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo

-nyl]pyrrolidinyl]hexanoic acid,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbo
-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-aminopropanoyl)pyrrolidin-2-yl]carbo
-nyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2
-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyr-
rolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-2-amino-3-carbamoylpropanoyl)pyrroli-
din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo
-nyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoic acid,
1-ethyl-2-[2-[((S)-1-[[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]
-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidn-2-yl]
-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrro-
lidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrroli-
din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo
-nyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoic aicd,
1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)-
amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-
carboxamidine,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo

-nyl]pyrrolidinyl]-(S)-2-[(methanesulfonyl)amino]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(4-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[(2-piperidinyl)carbonyl]pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]carbo-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-methyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 3-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-3-oxo-propanoate,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(2-carbamoylacetyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-4-oxobutanoate,
4-[(R)-2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-nyl]pyrrolidinyl]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[((R)-1-prop-2-enoylpyrrolidin-2-yl)carbonyl]pyrro-lidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[[(R)-1-(carbamoylmethyl)-5-oxopyrrolidin-2-yl]car-bonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
methyl-2-[2-[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]piperidinyl]acetate,
1-ethyl-2-[2-[(S)-1-[(3-piperidinyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

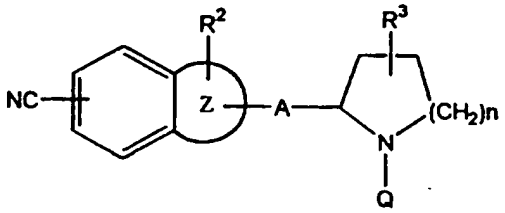
ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate,
ethyl 2-[2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate,
2-[2-[(S)-1-[((R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-1-(carbamoylmethyl)indole-6-carboxamidine, and
6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamidine.

4. A thrombin inhibitor composition containing as an active component the compound of formula (I) as defined in claim 1 or the pharmaceutically acceptable salt thereof together with a pharamceutcially acceptable carrier.

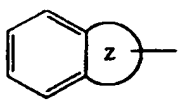
5. The thrombin inhibitor composition as defined in claim 4, which is useful for prevention and treatment of thrombosis.

6. The thrombin inhibitor composition as defined in claim 4, which is formulated into the oral preparation.

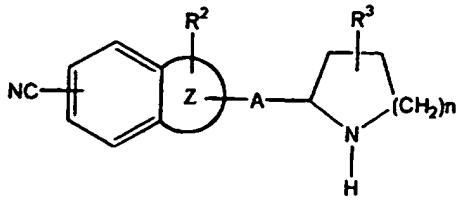
7. A process for preparing the compound of formula (I) as defined in claim 1 and its salts characterized in that:
(a) an amino-protecting group of a compound of formula (V):



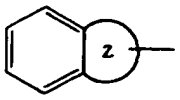
(V)

wherein 

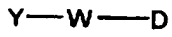
, R^2, R^3, A and n are defined as in claim 1 and Q represents an amino-protecting group, is removed to obtain a compound of formula (IV):



(IV)

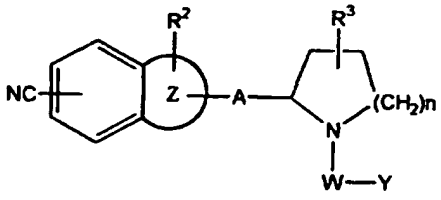
wherein  , R^2, R^3, A and n are defined as in claim 1;

(b) the nitrile compound of formula (IV) thereby obtained is reacted with a compound of formula (VI):

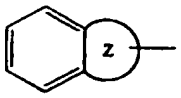


(VI)

wherein Y and W are defined as in claim 1 and D represents hydroxy or halogen, to obtain a compound of formula (III):



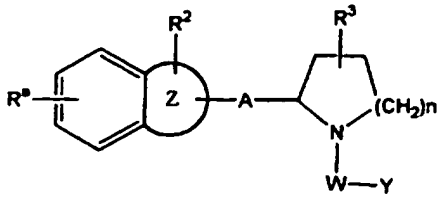
(III)

wherein  , R^2, R^3, A, Y, W and n are defined as in claim 1;

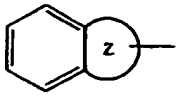
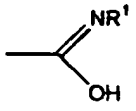
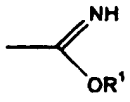
(c) the compound of formula (III) is reacted with an alcohol compound of formula (VII):

R^1OH (VII)

wherein R^1 is defined as in claim 1, in the presence of a hydrogen halide to obtain a compound of formula (II):

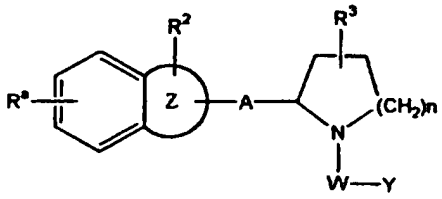


(II)

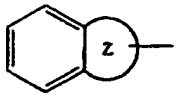
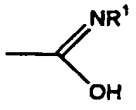
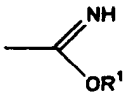
wherein  , R^2, R^3, A, Y, W and n are defined as in claim 1 and R^a is a group of formula  or  wherein R^1 is defined as in claim 1; and

(d) the compound of formula (II) is reacted with ammonia.

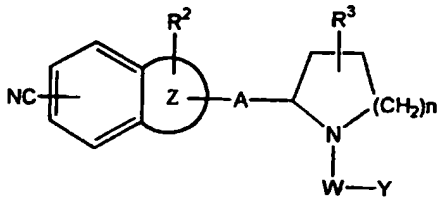
8. A compound of formula (II):



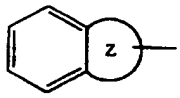
(II)

and its salt, wherein  , R^2, R^3, A, Y, W and n are defined as in claim 1 and R^a is a group of formula  or  wherein R^1 is defined in claim 1.

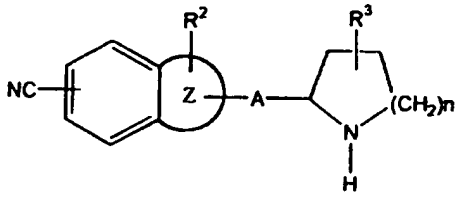
9. A compound of formula (III):



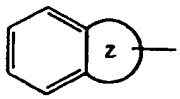
(III)

and its salt, wherein  , R^2, R^3, A, Y, W and n are defined as in claim 1.

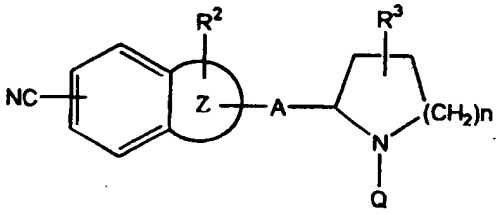
10. A compound of formul (IV):



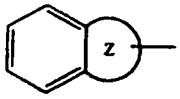
(IV)

and its salt, wherein  , R^2, R^3, A and n are defined as in claim 1.

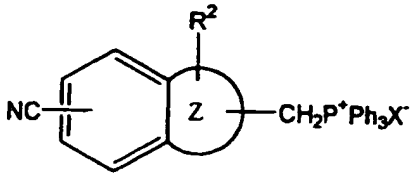
11. A compound of formula (V):



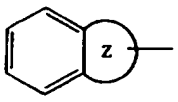
(V)

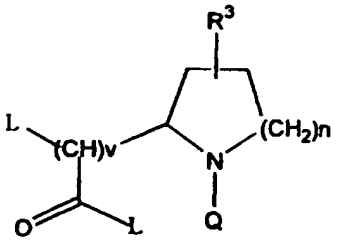
and its salt, wherein  , R^2, R^3, A and n are defined as in claim 1 and Q represents an amino-protecting group.

12. A process for preparing the compound of formula (V) as defined in claim 11 and its salt, which comprises reacting compound of formula (4):



(4)

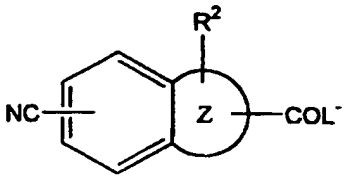
wherein  and R^2 are defined as in claim 1, with a compound of formula (5):



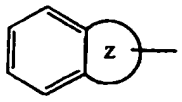
(5)

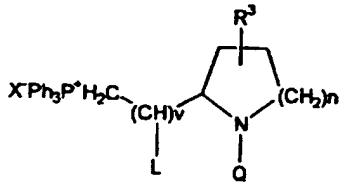
wherein R^3 and n are defined as in claim 1, two L groups may be same or different and represent hydrogen, alkyl, alkoxycarbonyl or alkoxy-carbonylalkyl, Q represents an amino-protecting group, X represents halogen, and v denotes an integer of 0 to 2.

13. A process for preparing the compound of formula (V) as defined in claim 11 and its salt, which comprises reacting a compound of formula (7):



(7)

wherein  and R^2 are defined as in claim 1 and L represents hydrogen, alkyl, alkoxycarbonyl or alkoxycarbonylalkyl, with a compound of formula (8):



(8)

wherein R^3 and n are defined as in claim 1, Q represents an amino-protecting group, X represents halogen, L represents hydrogen, alkyl, alkoxycarbonyl or alkoxycarbonylalkyl and v denotes an integer of 0 to 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00100

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 403/06,401/06,405/06,409/06,207/08,207/10; A 61 K 31/40,31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 403/00,405/00,409/00,207/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	Chemical Abstracts, Vol.125, No.11, 09 September 1996 (Columbus, Ohio, USA), page 28, column 1, abstract No.131628h, IWANOWICZ, E.J. et al.:"Derivatives of 5-amidine indole as inhibitors of thrombin catalytic activity", & Bioorg. Med. Chem. Lett. 1996, 6(12), 1339-1344 (Eng).	1-13
A	Chemical Abstracts, Vol.99, No.5, 01 August 1983 (Columbus, Ohio, USA), page 501, column 1, abstract No.38220d, KOWA CO., LTD.:"Phenyl esters", & Jpn. Kokai Tokkyo Koho JP 58 13,549 [83 13,549].	1-13
A	Chemical Abstracts, Vol.98, No.9, 28 February 1983 (Columbus, Ohio, USA), page 19, column 2, abstract No.65141q, TIDWELL, R.R. et al.:"Aromatic amidines. Comparison of their ability to block respiratory syncytial virus induced cell fusion and to inhibit plasmin, urokinase, thrombin, and trypsin", & J. Med. Chem. 1983, 26(2), 294-8.	1-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 August 1997 (07.08.97)	19 August 1997 (19.08.97)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer Telephone No. 1/53424/374

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00100

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol.123, No.23, 04 December 1995 (Columbus, Ohio, USA), page 50, column 1, abstract No.306203d, BAJUSZ, S. et al.:"Active site-directed thrombin inhibitors: α-hydroxyacyl-prolyl-arginals. New orally active stable analogs of D-Phe-Pro-Arg-H", & Bioorg. Med. Chem. 1995, 3(8), 1079-89 (Eng).	4-6
A	Chemical Abstracts, Vol.124, No.5, 29 January 1996 (Columbus, Ohio, USA), page 3, column 2, abstract No.44457n, KIMBALL, S.D.:"Challenges in the develop= ment of orally bioavailable thrombin active site inhibitors", & Blood Coagulation Fibrinolysis 1995, 6(6), 511-19 (Eng).	4-6
A	US 4 258 192 A (OKAMOTO) 24 May 1992 (24.05.92), claim 1; column 4, line 65 - column 6, line 44 (cited in the application).	4-6

INTERNATIONAL SEARCH REPORT

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International application No.

PCT/KR 97/00100

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		CA A2 1137469	14-12-82
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INTERNATIONAL SEARCH REPORT

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International application No.

PCT/KR 97/00100

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 97/00100

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